ANAESTHESIA FOR COLONIC SURGERY

Studies of the effects of anaesthetic techniques and other peri-operative factors on colonic anastomoses and colonic blood flow

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PREFACE

Many anaesthetists appear to regard the disruption of a colonic anastomosis either as an act of God, or of the surgeon. Surgeons tend to blame the patient, his general condition, the antibiotic regimen or the assistant. Although a number of important factors relating to the condition of the patient, the disease process and the surgical technique have been identified as being contributory to an increased incidence of anastomotic breakdown, no previous studies had investigated the effects on the colon of anaesthetic techniques or physiological changes brought about during anaesthesia or in the early post-operative period.

The work presented in this thesis was initiated by the clinical observations of an anaesthetist and a surgeon, who noticed that patients undergoing colonic anastomosis under spinal nerve block appeared to have a less complicated recovery than patients having similar procedures performed during general anaesthesia. This stimulated a retrospective clinical study which suggested that anaesthetic techniques might affect the incidence of anastomotic disruption after colonic surgery. A review of the literature supported the concept that blood supply to the colon might be an important determinant of anastomotic healing, and led to the development of an animal model in which colonic blood flow could be measured accurately, and in which a variety of pharmacological and physiological interventions related to anaesthesia and the peri-operative period could be investigated.

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Mr. Adair Peebles Brown was also responsible for the original observations on patients in his care who had undergone colonic anastomosis, and provided support and advice on surgical matters during the early parts of the investigations described in the thesis.

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I am very grateful to Professor Iain Ledingham who provided financial support within the University Department of Surgery at the Western Infirmary, Glasgow for all of the animal studies. He has also contributed enormously to my learning of methods of scientific investigation and writing.

Mr. Douglas Gilmour was jointly responsible for the development

of the dog model, and I am deeply grateful to him for teaching me practical aspects of surgery, for his ideas, and for our many hours of discussion.

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Ian Douglas, Dick Thomson, Steven Gray and Alan Fleming, the technicians in the Department of Surgery, were always patient and helpful during the eighteen months in which animal experiments were performed, and I am most grateful to them.

Dr. Fraser Davidson undertook the analysis of blood lactate and pyruvate concentrations, and I am very grateful to him and the staff of the Biochemistry Laboratory at Gartnavel General Hospital, Glasgow for their time and the use of their facilities.

The staff of the Medical Illustration Departments at the Western Infirmary, Glasgow and Leicester Royal Infirmary prepared all the figures, and I would like to express my thanks to them for their patience despite my persistent requests for minor alterations.

DECLARATION

The thesis was composed by myself and all referenced books and papers were consulted by me personally. The research was conducted between 1976 and 1979 while I was a Registrar in the Department of Anaesthesia in the Western Infirmary, Glasgow and subsequently a Research Fellow in the University Department of Surgery in the same institution.

I was responsible for all data collection in the retrospective study described in Chapter Three. Dr. H. Y. Wishart administered spinal nerve blocks to the patients investigated, and other anaesthetists in the Western Infirmary, Glasgow administered the general anaesthetics. Mr. D. A. Peebles Brown performed all the operations.

The investigations undertaken using the animal model were of necessity collaborative. The development of the animal model was undertaken jointly by Mr. D. G. Gilmour and myself, with the assistance of Mr. I. H. S. Douglas and his technicians, who calibrated the monitoring equipment, blood gas analyser and co-oximeter. Either Mr. Gilmour, Dr. A. P. Hothersall or myself anaesthetised the animals, and one of us, or one of the technicians, inserted the intravascular monitoring lines. Either Mr. Gilmour or myself undertook the intra-abdominal surgical preparation of the animals. We each performed approximately half of the laparotomies. Mr. Gilmour, Dr. Hothersall and myself undertook all other experimental procedures with the help of the technical staff when appropriate. Dr. P. W. Horton of the Department of Clinical Physics and Bioengineering of the West of Scotland Health Boards assisted

with the methodology of mathematical analysis of the washout curves, with the methodology of the microsphere technique and with the methodology used for studying Ostwald solubility coefficients. Dr. D. F. Davidson of the Department of Biochemistry, Gartnavel General Hospital, Glasgow measured blood concentrations of lactate and pyruvate.

All the statistical analysis of data presented in the thesis was undertaken by myself. A word processor and I prepared all the text and tables, and any typographical errors or errors of format are my own.

The following publications include work presented in the thesis:

Aitkenhead, A. R., Wishart, H. Y., and Peebles Brown, D. A. (1978). High spinal nerve block for large bowel anastomosis. A retrospective study.
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Cardiovascular Research, **14**, 11 - 20.

Aitkenhead, A. R., Gilmour, D. G., Hothersall, A. P., and Ledingham, I. McA. (1980). Effects of subarachnoid spinal nerve block and arterial P_{CO_2} on colon blood flow in the dog.
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Gilmour, D. G., Aitkenhead, A. R., Hothersall, A. P., and Ledingham, I. McA. (1980). The effect of hypovolaemia on colonic blood flow in the dog.
British Journal of Surgery, **67**, 82 - 84.

Gilmour, D. G., Aitkenhead, A. R., and Ledingham, I. McA. (1980). Results of ^{133}Xenon clearance studies in the greyhound colon. In: Gastrointestinal Mucosal Blood Flow, ed. Fielding, L. P., pp. 219 - 229. Edinburgh: Churchill Livingstone.

Aitkenhead, A. R. (1982). Complications following large bowel surgery.
Regional Anesthesia, **7**, S99 - S104.

Aitkenhead, A. R. (1984). Anaesthesia and bowel surgery.
British Journal of Anaesthesia, **56**, 95 - 101.

Aitkenhead, A. R. (1984). Anaesthesia for bowel surgery.
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ABBREVIATIONS

a	arterial
AP	arterial pressure
C	content
^{o}C	degree(s) Centigrade
cm^{-3}	per cubic centimetre
CO_2	carbon dioxide
CBF	colonic blood flow
CO	cardiac output
CSF	cerebrospinal fluid
CVR	colonic vascular resistance
d	density
dl^{-1}	per decilitre
dP/dt	rate of rise of pressure
ECG	electrocardiograph
g	gram(s)
100 g^{-1}	per 100 grams
hr	hour(s)
$[H^{+}]$	hydrogen ion concentration
Hb	haemoglobin
HR	heart rate
i.m.	intramuscular
IPPV	intermittent positive pressure ventilation
i.v.	intravenous
k	clearance constant
kPa	kilo-Pascal(s)
kg	kilogram(s)

kg^{-1}	per kilogram
^{85}Kr	krypton-85
$litre^{-1}$	per litre
L	lumbar interspace
LDH	lactate dehydrogenase
MAC	minimum alveolar concentration
MAP	mean arterial pressure
min	minute(s)
min^{-1}	per minute
mg	milligram(s)
ml	millilitre(s)
mmol	millimole(s)
mm Hg	millimetres of mercury
n	number
NAD	nicotinamide adenine dinucleotide
NADH	dihydronicotinamide adenine dinucleotide
O_2	oxygen
p	probability
P	partial pressure
pH	$- \log [H^+]$
Q_t	cardiac output
r	correlation coefficient
RAP	right atrial pressure
S	sacral interspace
sd	standard deviation
sec	second(s)
sem	standard error of the mean
t	t-statistic

T	thoracic interspace
^{85}Sr	strontium-85
TPR	total peripheral resistance
$\mu_{t/b}$	tissue/blood partition coefficient
µCi	micro-Curie(s)
µm	micrometre(s)
µmol	micromole(s)
v	venous
^{133}Xe	xenon-133
yr	year(s)

ABSTRACT

The disruption of an anastomosis is the most significant single cause of morbidity and mortality following colonic surgery. A number of factors are known to increase the risk of anastomotic breakdown in the colon, and these are reviewed. The physiology of the intestines is discussed, with particular emphasis on the effects on the bowel of anaesthetic drugs, techniques employed during anaesthesia, and other factors pertaining to the peri-operative period.

A retrospective clinical study of patients who had undergone colonic anastomosis either during spinal nerve block with a light general anaesthetic or under conventional general anaesthesia is presented and the findings discussed. There appeared to be a trend suggesting that spinal nerve block might result in a rather lower incidence of anastomotic breakdown.

Because oxygen delivery is an important factor in wound healing, and because anastomotic healing is known to be impaired by an inadequate blood flow, an animal model was developed for the measurement of colonic blood flow. The model was designed in such a way that the integrity of the nerve and blood supply was maintained, and was validated by comparison with other techniques.

The effects of a number of factors of relevance to the peri-operative period were investigated using the model. Hypocapnia was found to reduce colonic blood flow, and hypercapnia to increase it. The increase in flow associated with hypercapnia diminished over a 60 min period. Moderate hypovolaemia decreased blood flow to the colon. Spinal nerve block and halothane both resulted in increased flow, although i.v. methoxamine or hypovolaemia during spinal nerve block produced substantial reductions. The clinical relevance of these findings is discussed.

CHAPTER ONE

INTRODUCTION

[1.1] BACKGROUND

Significant, life-threatening morbidity occurs in up to 24% of patients undergoing resection and anastomosis of the colon (Schrock, Deveney and Dunphy, 1973). The commonest single cause of serious morbidity is dehiscence of the anastomosis itself. Clinical evidence of anastomotic disruption occurs in 5 to 16% of patients following colonic resection (Dunphy, 1970; Whitaker, Dixon and Greatorex, 1970), although radiological evidence (by barium or Gastrografin enema) of anastomotic breakdown may be found in up to 69% of patients undergoing anterior resection of the rectum (Goligher, Graham and de Dombal, 1970). Disruption of the anastomotic suture line carries a mortality of 33%, and is responsible for 37% of all deaths associated with colonic anastomoses.

[1.2] FACTORS AFFECTING INCIDENCE OF ANASTOMOTIC DEHISCENCE

A number of factors are known to increase the incidence of anastomotic dehiscence in the colon. Many of these were defined by Schrock, Deveney and Dunphy (1973) in a retrospective study of 1703 colonic anastomoses performed over a 20 year period. The overall morbidity was 24%, and the total incidence of anastomotic breakdown was 4.5%. Wound infection developed in 7.7% of cases, cardiovascular complications in 5.1%, and miscellaneous other complications in a total of 12%. The overall mortality was 4.0%, and 37% of the deaths were due to anastomotic leakage. The mortality in patients with an-

astomotic dehiscence was 33% compared with 2.6% in patients with an intact anastomosis.

Detailed analysis of their results permitted the authors to identify factors associated with an increased risk of anastomotic breakdown. They found that the risk increased progressively with age in patients of 60 years and over. Pre-operative anaemia, defined as a haematocrit of less than 35%, doubled the risk of dehiscence, and the administration of pre-operative radiation therapy quadrupled it. Resections carried out as emergency procedures were associated with an incidence of breakdown twice as great as the incidence in those undertaken electively. The presence of intraperitoneal infection at the time of surgery increased the risk of anastomotic disruption three-fold. Anterior resection of the rectum was associated with a high incidence (9.2%) of anastomotic disruption compared with operations involving only the colon (3.5%). Patients undergoing surgery because of carcinoma of the colon had a higher incidence of anastomotic leakage than those operated upon for benign disease; residual carcinoma at the margins of the suture line carried a particularly poor prognosis.

Intra-operative hypotension, defined by the authors as a decrease in systolic arterial pressure by at least 50 mm Hg below baseline for 15 min or longer, was associated with a significantly increased incidence of anastomotic breakdown. The cause of hypotension was not defined, although it is likely that it was associated with haemorrhage, as it was also noted that the anastomotic breakdown rate increased in proportion to the number of units of blood transfused. A further observation was that patients who were both anaemic and required intra-operative blood transfusion had the

highest incidence of anastomotic breakdown of any subgroup in the series. For example, 31.8% of anaemic patients who required intra-operative transfusion of four or more units of blood suffered anastomotic leakage, compared with 3.1% of patients who were not anaemic and who required no more than one unit of blood to be transfused.

The surgical technique is of importance in determining the fate of an anastomosis. Inverting techniques are superior to everting techniques (Rusca, Bornside and Cohn, 1969; Goligher et al., 1970), although it appears that there is little difference in outcome if one layer of sutures is employed rather than two. Tagart (1981) reviewed reports of differences in anastomotic breakdown rates following low colonic or rectal anastomoses using either a stapling technique or conventional sutures, and concluded that although some surgeons appeared to have improved their results using the stapling gun, there was little real difference between the techniques. However, stapling guns permit anastomoses to be constructed in very low positions within the pelvis where a suturing technique would not be possible.

Schrock, Deveney and Dunphy (1973) found no relationship between the incidence of anastomotic breakdown and nutritional status, the presence of disease of the heart, lungs or kidneys, pre-existing diabetes mellitus, extracolonic malignancies, or concurrent medication other than steroids. Steroid therapy was associated with a small but statistically insignificant increase in dehiscence rate. No relationship between anastomotic breakdown rate and the choice of bowel preparation or antibiotic therapy was demonstrable. Surprisingly, the experience of the surgeon did not affect the rate of anastomotic complications.

Clearly, adverse prognostic factors are likely to be additive

in their effect on the outcome of a colonic anastomosis. Indeed, Morgenstern and others (1972) have devised a weighting table (Table 1.1) to assess the risk, and advisability, of colonic resection.

[1.3] DEFINITION OF AREAS WHICH WARRANT INVESTIGATION

Although many risk factors do not lend themselves to manipulation by medical staff (e.g. age, aetiology of colonic disease, segment of colon to be resected), it is possible that the likelihood of a successful outcome following an anastomosis might be improved if the conditions for anastomotic healing are optimised, and conversely that the incidence of anastomotic breakdown might be increased if they are impaired. There would appear on theoretical grounds to be two important mechanisms which deserve attention in this respect, and which could be influenced by appropriate medical intervention.

1) Physical pressures, either longitudinally resulting from increased tension in the longitudinal muscles of the colon, or outwardly as the result of increased intraluminal pressure, might produce excessive traction across an anastomosis, and rupture a recently constructed suture line. The prevention of such physical forces by careful selection during the peri-operative period of pharmacological agents known to increase them might reduce the risk of disruption of an anastomosis before healing has produced adequate adhesion between the apposed edges.
2) Oxygen supply may influence anastomotic healing. Anaemia, hypotension probably associated with haemorrhage and vasoconstriction, and blood transfusion increase the risk of anastomotic disruption (vide supra). Remote trauma, hypovolaemia and hypoxia all have adverse effects on wound healing in general (Zederfeldt, 1957;

TABLE 1.1 Indications for staging of resections (i.e. avoiding primary resection and anastomosis) in low anterior resection for carcinoma or segmental resections for diverticulitis (Morgenstern et al., 1972).

	Weighting factor
Systemic factors	
Advanced age	+
Obesity	+
Malnutrition	++
Coagulopathy	+
Steroid dependence	++
Uraemia	++
Diabetes mellitus	+
Local factors	
Abscess, perforation, fistula, or peritonitis	++
Technical difficulty	++
Poor preparation, faecal soiling	+

Total score	++ or +++	Relative indication for staging
	++++	Absolute indication for staging

Stephens and Hunt, 1971; Hunt and Pai, 1972), probably as a result of a reduction in oxygen availability. Factors which decrease oxygen availability to an anastomosis might result in a critical degree of hypoxia, causing either necrosis or failure of the normal healing processes. Conversely, increased oxygen availability might help to protect a potentially hypoxic anastomosis and increase the probability of its successful healing.

While the link between these mechanisms and the incidence of anastomotic breakdown remains to be proved, their significance lies in the ability of medical staff, and in particular the anaesthetist, to influence them during the peri-operative period. Drugs used in the peri-operative period, and alterations in the cardiovascular system induced by anaesthetic techniques, may affect both mechanisms.

[1.4] AREAS OF INVESTIGATION UNDERTAKEN

The investigations detailed in the succeeding chapters were undertaken in an attempt to elucidate the effects of anaesthetic technique on the outcome of colonic anastomoses, and to define the alterations in colonic blood flow, which in turn influences oxygen supply, resulting from some of the events which may arise during the peri-operative period.

Chapter Two outlines the physiology of the gastrointestinal tract and summarises previous reports of investigations in this area. A retrospective study of colonic anastomoses constructed either during conventional general anaesthesia or during subarachnoid or extradural spinal nerve block is presented in Chapter Three. Chapter Four describes the methodology used in development of an animal model

for measurement of colonic blood flow and oxygen consumption, and presents the baseline values obtained under resting conditions. A series of experiments undertaken using the animal model to investigate alterations in blood flow and oxygen supply to the colon associated with changes in arterial carbon dioxide tension, hypovolaemia, spinal nerve block and the administration of halothane are detailed in Chapters Five to Eight. General discussion of the results of these studies, and conclusions which may be derived, are contained in Chapter Nine.

CHAPTER TWO

THE EFFECTS OF ANAESTHESIA AND SURGERY ON THE BOWEL

[2.1] INTRODUCTION

By far the greatest proportion of major procedures undertaken by general surgeons involves surgery of the gastrointestinal tract. Perhaps because of its frequency or its lack of specialist status, bowel surgery is regarded by most anaesthetists as requiring little other than routine anaesthesia, and little attention is paid to the consequences of anaesthetic drugs or techniques on either the outcome of the procedure or the post-operative course of the patient.

Many factors may influence the post-operative course of a patient undergoing gastrointestinal surgery, including the nature of the lesion requiring operation, pre-existing medical disorders and drugs taken for their treatment, electrolyte imbalance, pre-operative anaemia or malnutrition, the operative technique employed, and the technical abilities of the surgeon.

However, the anaesthetic technique and drugs employed by the anaesthetist may have significant effects on the bowel. Although treatment initiated by the anaesthetist may influence post-operative complications such as ileus, the major risk in terms of morbidity and mortality involves the disruption of anastomoses. This is of particular concern after resection of either the oesophagus or colon. Anastomotic disruption is much commoner in these structures than in the small intestine, probably as a result their relatively poor blood supply, or difficulties in maintaining a satisfactory blood supply after resection. Anastomotic breakdown occurs in approximately 28% of

patients after oesophageal resection (Skinner, 1976). Overall mortality is approximately 23%, half the deaths being attributable to anastomotic breakdown (Chassin, 1978). However, resection of the colon is performed much more frequently than surgery to the oesophagus. Although the incidence of clinically apparent anastomotic breakdown is lower (5 to 20%) following colonic resection, the mortality in patients whose colonic anastomosis shows clinical evidence of disruption is approximately 35% (Irvin and Goligher, 1973; Schrock, Deveney and Dunphy, 1973). Thus the total morbidity and mortality resulting from colonic surgery is considerable.

It appears possible to relate the most important effects resulting from administration of drugs during anaesthesia and in the post-operative period to alterations in gut contractility or changes in blood flow and oxygen delivery.

[2.2] BOWEL CONTRACTILITY

Normal contractility of the bowel is dependent on neural and humoral factors. Motility is increased by cholinergic stimulation and inhibited by impulses transmitted through alpha and beta adrenergic receptors. Alpha receptors are predominant in the stomach and small bowel, while beta receptors are responsible for adrenergic inhibition in the colon. In addition, there may be some alpha receptors which exert their action via cholinergic ganglia. These may be purinergic nerves, with adenosine triphosphate (ATP) as the transmitter (Burnstock, 1972). A number of circulating peptides, notably motilin, gastrin and cholecystokinin also stimulate contractility, particularly in the colon.

Following laparotomy, the small intestine normally regains its

motility within a few hours (Rennie et al., 1980). The stomach begins to empty after approximately 24 hr. The colon, however, may not resume its normal motility for 48 hr or longer, and it is likely that decreased motility in the colon is mainly responsible for post-operative ileus. Peritonitis and electrolyte abnormalities, particularly hypokalaemia, prolong ileus. However, the traditional view that the gut was paralysed because of handling at the time of surgery is no longer tenable. Electrical activity within the bowel remains normal after laparotomy (Rennie et al., 1980; Carmichael, Weisbrodt and Copeland, 1977). The ability of gastrointestinal smooth muscle to contract is not impaired, and it retains its responsiveness to both extrinsic electrical (Wangensteen, 1955) and chemical (Neely and Catchpole, 1971) stimulation.

However, contractility is inhibited by a combination of factors; increased sympathetic activity, increased stimulation of dopaminergic receptors, and decreased levels of motilin. Much of this inhibition can be attributed to catecholamine release, either due to increased sympathetic tone, or as a result of increased levels of circulating catecholamines. Plasma noradrenaline concentrations increase significantly during and after surgery conducted under general anaesthesia (Halter, Pflug and Porte, 1977), despite conventional systemic analgesia (Fell, Chmielewski and Smith, 1982). In addition, motilin levels are decreased during anaesthesia and surgery, although an increase occurs between 6 and 24 hr post-operatively. Peak levels correspond with the return of normal colonic activity (Rennie et al., 1980).

Bowel distension, which may result from decreased motility, may itself cause impaired bowel contractility, due both to intestino-in-

testinal reflexes and interference with perfusion (Youmans, 1952). If the lumen is distended to produce pressures below 30 mm Hg, blood flow may increase (Hanson, 1973; Chou and Grassmick, 1978) or decrease (Hanson and Moore, 1969a). Higher pressures (40 - 70 mm Hg) result in significant decreases in blood flow (Chou and Grassmick, 1978; Hanson and Moore, 1969a). The blood flow changes induced by distension occur predominantly in the mucosa (Ruf et al., 1980). Distension may lead to increased intraluminal pressure, endangering intestinal anastomoses. This may be a particular risk in patients with diverticular disease, as the "normal" colon remaining after resection of the diseased area does not react normally to distending forces (Parks, 1970). Abdominal distension resulting from prolonged ileus may contribute to wound dehiscence, and, by producing diaphragmatic splinting, can impair basal ventilation and increase post-operative respiratory complications.

Water and electrolyte absorption in the small bowel is impaired for more than 30 hr after handling of healthy bowel (Bunch, 1971). Water, sodium and potassium are secreted into the ileum in the presence of intestinal obstruction or ileus (Grace, 1971), and factors which prolong ileus thus alter intravenous fluid and electrolyte requirements in the post-operative period.

Increased contractility may produce an increase in motility, or may be unco-ordinated, resulting in segmentation of the bowel, and the development of high intraluminal pressures. Longitudinal traction resulting from an increase in muscle contraction may produce excessive forces across an anastomotic suture line. Rhythmic contractions may increase or decrease blood flow to the bowel, although increases are confined to the muscle layer (Chou and Gallavan, 1982).

Drug-induced tonic contractions decrease blood flow and increase vascular resistance.

Increased contractility may thus rupture an anastomosis either by direct force or as a result of high intraluminal pressures, and may reduce perfusion to the bowel wall. The latter may be of importance not only to the integrity of an anastomosis, but also to the viability of areas of ischaemic bowel.

[2.3] BLOOD FLOW

[2.3.1] General considerations

It is known that factors associated with reduced blood supply or oxygen carriage have adverse effects on wound healing in general. Stephens and Hunt (1971) found that the P_{O_2} in fluid aspirated from experimental wounds in rats was proportional to the inspired oxygen concentration, and that tensile strength of the wounds increased with increasing P_{O_2}. They suggested that the rate of healing was governed by the oxygen supply, and that wound healing was likely to be impaired in patients with respiratory failure or poor perfusion states. Hunt and Pai (1972) found that the production of connective tissue and collagen in experimental wounds was related directly to the oxygen supply. The importance of maintenance of an adequate blood supply to intestinal anastomoses was emphasised by Everett (1974). In his view, the blood supply to the bowel ends is inadequate in most cases in which gross leakage occurs from an anastomotic suture line, and he noted that the blood supply to the antimesenteric border of the bowel is particularly vulnerable.

Although surgical impairment of blood supply is seldom of major importance in surgery of the stomach or small intestine, it is often

difficult to ensure adequacy of blood flow after resection of the colon, particularly in the sigmoid region or in the rectum, or after mobilisation of colon for anastomosis to the oesophagus. In these situations particularly, further reductions in oxygen supply, either due to hypoxaemia, inadequate oxygen carriage, or impairment of blood supply, may lead to hypoxia at the anastomotic suture line. It is likely that even a relatively short period of severe local hypoxia may cause severe damage to an anastomosis.

Factors which improve blood flow to the bowel may maintain oxygen delivery to an anastomosis and permit normal healing to take place. Whitaker (1968) concluded from a study of blood flow in a small number of patients that blood supply was the most important single factor related to healing of colonic anastomoses.

[2.3.2] Blood supply to small intestine

Blood flow in the splanchnic and mesenteric circulations are influenced predominantly by the autonomic nervous system. Alpha-adrenergic stimulation produces vasoconstriction, while $ß_2$-stimulation results in vasodilatation (Kerr and Swan, 1981). Dopamine is known to act at two receptors (Pawlik et al., 1976); vasoconstriction results from stimulation of dopaminergic receptors and this predominates over mild vasodilatation produced by an action at $ß_2$-adrenergic receptors. Parasympathetic stimulation increases blood flow secondary to increased metabolism resulting from secretory and motor activity. Under normal circumstances, autoregulation maintains blood flow to the small intestine. During prolonged sympathetic stimulation, the mesenteric circulation exhibits "escape". Autoregulatory escape, a different entity from autoregulation, re-

sults from an intrinsic ability of the intestinal vascular bed to escape from a strong vasoconstrictive stimulus such as sympathetic nerve stimulation or catecholamine infusion. It is thought to be due to a combination of a transient transmutation of receptors to a refractory state and to release of a local vasodilator agent. The initial decrease in blood flow resulting from vasoconstriction is not sustained, and after a few minutes blood flow begins to increase towards normal levels (Shanbour and Jacobson, 1971).

In severe stress states, a number of vasoconstrictor substances are released, including catecholamines, angiotensin II and vasopressin. All of these reduce visceral blood flow.

The mucosa is particularly susceptible to ischaemia. Sympathetic stimulation reduces mucosal perfusion in order to maintain blood flow to the muscularis. The circulation in the villi of the small intestine consists of an inflow arteriole and an outflow venule, which act as a countercurrent exchanger for oxygen, and which can, in low-flow states, result in a severe reduction in oxygen tension in the capillaries at the tip of the villus (Lanciault and Jacobson, 1976).

[**2.3.3**] Colonic blood supply

Blood flow to the colon is less than that to the small intestine. Bond, Prentiss and Levitt (1980) found that total blood flow to the colon in the dog was 34 ml min^{-1} 100 g^{-1}, compared with values of 58 and 38 ml min^{-1} 100 g^{-1} to jejunum and ileum respectively.

Intrinsic control of blood flow within the colon is usually attributed to metabolic and myogenic factors. The metabolic hypo-

thesis suggests that tissue metabolism and vascular smooth muscle constitute a local control system in which arteriolar and precapillary sphincter tone are modulated by vasodilator metabolites released from cells. The myogenic theory is based on the assumption that vascular resistance is directly proportional to transmural pressure at the arteriolar level due to the effect of stretch on contractility of vascular smooth muscle.

Although early studies suggested that intrinsic control of the colonic vasculature was due solely to myogenic factors (Hanson and Johnson, 1967), more recent evidence suggests that both myogenic and metabolic factors are involved (Kvietys, Miller and Granger, 1980). However, autoregulation within the colon is poor. The incidence of autoregulation in sympathetically denervated preparations is about 20%, compared to 72% in the small intestine (Hanson and Johnson, 1967). Although total colonic blood flow is poorly controlled, flow to the mucosa is well maintained until perfusion pressure decreases to less than 40 mm Hg (Kvietys and Granger, 1982). The colon is capable of increasing oxygen extraction from the normal 15 - 20% to approximately 50% if colonic blood flow decreases (Kvietys, Miller and Granger, 1980), thus offering some protection against hypoperfusion. Autoregulation and oxygen extraction are impaired by distension (Hanson and Moore, 1969b) and by a lack of metabolic stimulation from the presence of bowel contents (Kvietys and Granger, 1981).

In addition to intrinsic mechanisms of vascular control, the colon receives extrinsic neural regulation from the sympathetic and parasympathetic nervous systems. Stimulation of sympathetic postganglionic fibres originating from the splanchnic and lumbar colonic nerves results in vasoconstriction, causing a reduction in colonic

blood flow. This effect is transient, however, and is followed by a partial recovery of flow due to autoregulatory escape, similar to that seen in the small bowel (see section [2.3.2]). However, in the colon, the escape is less complete, and blood flow to both the mucosa and muscle layers remains depressed (Kvietys and Granger, 1982). The parasympathetic nerve supply to the colon is derived from the vagus (right hemicolon) and from the pelvic nerves. Stimulation of the vagus does not appear to affect colonic blood flow, while pelvic nerve stimulation results in an intense but transient hyperaemia, resulting in preferential distribution of flow to the mucosa (Hultén, 1969). This effect is combined with an increase in motility, and is presumably related to the metabolic expectations which normally cause colonic parasympathetic stimulation.

Noradrenaline and adrenaline, as would be anticipated, increase colonic vascular resistance and decrease colonic blood flow and oxygen uptake, while isoprenaline increases blood flow but has no effect on oxygen uptake (Immink, Beijer and Charbon, 1976; Hultén, 1969).

[2.4] PERI-OPERATIVE FACTORS AFFECTING THE BOWEL

[2.4.1] Disease and surgery

Bowel motility is reduced following any major trauma, including surgery (see section [2.2]). Blood flow to stomach, small bowel and colon is not altered significantly during laparotomy in dogs (Bond, Prentiss and Levitt, 1980), although "laparotomy" in this series of experiments consisted only of a midline incision, with no manipulation of intra-abdominal structures. Eade and Ginn (1978) reported a slightly reduced cardiac output and small bowel blood flow in dogs following laparotomy. Trauma results in an increase in splanchnic

oxygen consumption (Wilmore et al., 1980).

Whitaker (1968) noted that atherosclerosis at the origin of the inferior mesenteric artery was present in some older patients, and that there was a strong negative correlation between inferior mesenteric artery blood flow and increasing age.

Colonic blood flow is increased in severe acute ulcerative colitis, but is reduced in the quiescent stage of the disease. Ileal Crohn's disease results in a decrease in blood flow to the affected area (Hultén et al., 1977). Whitaker (1968) found an increased inferior mesenteric artery flow in patients with Crohn's disease, but noted that the mean age of these patients was very much less than that of other patients in whom mesenteric blood flow was measured. It was unclear whether the disease or the age of the patients was more significant in determining blood flow.

[2.4.2] Haemodynamic factors

A number of human and animal studies have demonstrated harmful effects on the gut of low-flow states (Chiu et al., 1970; Haglund, 1973; Haglund et al., 1975). The mucosa is particularly sensitive to ischaemia, and the degree of mucosal damage is inversely proportional to the blood supply. Whitaker, Dixon and Greatorex (1970) and Vatner (1974) showed that mesenteric artery flow in dogs decreased significantly in response to haemorrhage of 10-15% of blood volume, and that retransfusion of the shed blood did not necessarily restore blood flow to normal. Whitaker, Dixon and Greatorex (1970) and Schrock, Deveney and Dunphy (1973) found in clinical studies that both blood loss and hypotension were associated with increases in frequency of anastomotic dehiscence following colonic resection.

Increased intestinal blood flow does not alter intestinal motility (Chou and Dabney, 1967). However, partial ischaemia or hypoxaemia induce an immediate increase in contractions, which lasts for up to 5 min, followed by a reduction in contractility. The duration of this quiescent period depends on the period of ischaemia; if an adequate circulation is restored in less than 4 hr, then contractility resumes a normal pattern within 5 min. Longer periods of ischaemia result in permanent damage to the myenteric nerve plexus, and although contractility is restored, its pattern remains abnormal for at least 28 days (Chou and Gallavan, 1982; Szurzewski and Steggerda, 1968).

The effects of haemoglobin concentration on anastomotic healing are controversial. Bailey and others (1979) found that wound healing in diabetic digital amputations was better in patients whose haemoglobin concentration was less than 12 g dl^{-1} than in those with a haemoglobin concentration exceeding 13 g dl^{-1}. They attributed this difference to impairment of the microcirculation by increased blood viscosity in the patients with a higher haemoglobin concentration, and to the possibility that these patients might be more prone to develop intracapillary thrombosis. Gruber (1970) demonstrated that oxygen delivery to tissues, which is dependent on oxygen carrying capacity (and thus haemoglobin concentration) and blood flow, was maximal at a haematocrit of 35% (corresponding to a haemoglobin concentration of 11 g dl^{-1}), and decreased considerably if the haematocrit was higher or lower. Based on these reports, Tagart (1981) recommended haemodilution to a haemoglobin concentration of around 12 g dl^{-1} prior to colonic resection and anastomosis, and maintenance of the concentration at approximately 11 g dl^{-1} during

the post-operative period. However, the evidence of benefit from this technique was inconclusive.

In contrast, Schrock, Deveney and Dunphy (1973) found that the frequency of leakage from colonic anastomoses performed on patients with a haematocrit of less than 35% was almost double that in other patients.

[2.4.3] Intravenous anaesthetic agents

Thiopentone and minaxolone increase electrical and mechanical activity in the duodenum and jejunum, but not in the stomach or ileum, and may be contraindicated in patients with a recently constructed intestinal anastomosis (Healy et al., 1981). Atropine premedication prevents the increase in contractility associated with the administration of these agents. Ketamine produces no effect on gastrointestinal activity. Diazepam reduces gastric emptying and increases small bowel transit time (Birnbaum, Ben-Menachem and Schwartz, 1970), actions which may be undesirable in the post-operative period.

[2.4.4] Volatile anaesthetic agents

Motility of stomach, jejunum and colon is decreased by concentrations of chloroform or ether sufficient to produce surgical anaesthesia (Miller, 1926). Similar effects have been noted in dogs anaesthetised with cyclopropane (Weisel, Youmans and Cassels, 1938). In similar experiments with halothane, Marshall, Pittinger and Long (1961) found that contractility in stomach and jejunum was abolished, and in colon markedly decreased, by halothane administered at a concentration which abolished reflex movement to noxious stimuli. The

effects on bowel contractility of all the volatile agents studied diminish as anaesthesia lightens, and motility returns to normal by the time the patient regains consciousness. These effects seem unlikely to influence the post-operative course, although they may modify the effects of other drugs (vide infra).

Vatner and Smith (1974) found that anaesthesia with halothane 1% increased mesenteric vascular resistance in dogs by up to 78% and reduced mesenteric blood flow by a mean of 59%. However, their technique of measurement was invasive, and probably interfered with the integrity of the sympathetic nervous supply to the mesenteric circulation. In a model of shock induced by bowel ischaemia, rats anaesthetised with halothane had a greater likelihood of survival than those receiving ketamine anaesthesia (Bavister and Longnecker, 1979).

Methoxyflurane has been found to reduce splanchnic blood flow by 50% (Libonati et al., 1973).

[2.4.5] Nitrous oxide

Because of its greater blood/gas solubility coefficient, nitrous oxide diffuses into air-containing body cavities much more rapidly than nitrogen diffuses out. Eger and Saidman (1965) found that intestinal gas volume in dogs increased by 100 - 200% in 4 hr during the administration of 70 - 80% nitrous oxide, and suggested that nitrous oxide anaesthesia is relatively contraindicated in patients with intestinal obstruction. Nitrous oxide-induced distension may hamper abdominal wall closure, and may predispose to post-operative ileus. The theoretical maximum increase in gas volume may be reduced from 400 to 100% by reducing the alveolar nitrous oxide concentration from 80 to 50% (Lewis, 1975).

[2.4.6] Neostigmine

The effects of neostigmine on bowel contractility are well known. Motility is increased in all parts of the gastrointestinal tract, although, since its action is due to cholinesterase inhibition, its effects on gastric motility are reduced after vagotomy. Increased intraluminal pressure and propulsive activity in the small bowel (Bårány and Jacobson, 1964) and an increase of more than 200% in colonic and rectal activity (Wilkins et al., 1970) have been reported in conscious subjects. Atropine or glycopyrronium administered before neostigmine do not prevent the increase in intraluminal pressure in conscious subjects. Child (1984) investigated patients with a chronic sigmoid colostomy, and found intraluminal colonic pressures ranging from 30 to 100 mm Hg following i.v. neostigmine 2.5 mg administered 5 min after either i.v. atropine 1.2 mg or glycopyrronium 0.6 mg.

Patients with diverticular disease appear to be particularly sensitive to the effects of neostigmine. Painter and Truelove (1964b) reported a fourfold increase in the frequency of pressure waves exceeding 50 mm Hg in the sigmoid colon of normal individuals in response to the i.m. injection of neostigmine 1 mg, compared with a 600% increase in patients with diverticular disease. Areas of unaffected bowel in patients with diverticular disease also exhibit an exaggerated response to the administration of neostigmine (Parks, 1970).

Neostigmine reduces mesenteric blood flow by 30-50% (Whitaker, 1968), the reduction being associated with each exaggerated contraction induced by its administration. Atropine given i.v. before neostigmine protects partially against the decrease in blood flow.

Bell and Lewis (1968) investigated retrospectively the effects of neostigmine in patients undergoing ileorectal anastomosis for ulcerative colitis. No details were provided by the authors concerning the risk factors present in the two groups of patients, who received either a nitrous oxide-oxygen-cyclopropane anaesthetic, or a nitrous oxide-oxygen-relaxant technique with the effects of the relaxant antagonised using neostigmine 2.5 mg administered with atropine 1.2 mg. The factors determining the choice of anaesthetic technique are not known. The incidence of anastomotic breakdown, detected by barium enema, was 36% in those patients who received neostigmine, and 4% in those in whom neostigmine was not required. The incidence of clinical leakage was not reported. Any potentially beneficial effect of cyclopropane itself was discounted by the authors.

However, Wilkins and others (1970) found that neostigmine produced a significant increase in colonic or rectal activity in only 20% of patients anaesthetised with nitrous oxide alone, irrespective of whether atropine was administered before or with the anticholinesterase. Ileal activity was increased significantly. Halothane was found to abolish totally the increased activity associated with neostigmine in colon and rectum.

Whitaker (1968) noted that, in the intact colon of dogs, neostigmine produced violent contractions, intraluminal pressures of up to 75 mm Hg, and elevated tension in the longitudinal muscle. However, when an anastomosis had been performed, depriving the proximal segment of its parasympathetic nerve supply from the nervi erigentes, the effect of neostigmine was prominent only in the portion of colon distal to the anastomosis. Atropine administered

beforehand greatly reduced the effects of neostigmine. In a clinical study, Whitaker found that there was no difference in the mean dose of neostigmine administered to patients whose colonic anastomosis subsequently leaked compared with those whose anastomosis remained intact.

In summary, it would appear that, in anaesthetised patients, the effects of neostigmine on bowel contractility predominate in the small intestine. These effects are partly antagonised by atropine, and abolished by halothane. The drug should be used with caution, particularly in patients with diverticular disease, and in those undergoing ileorectal anastomosis.

[**2.4.7**] Opioid analgesics

The administration of morphine results in alterations in bowel contractility and blood flow. Painter and Truelove (1964a) demonstrated that morphine doubled the frequency of contractions resulting in intraluminal pressures between 20 and 50 mm Hg in the sigmoid colon of normal individuals. In patients with diverticular disease, intracolonic pressures in excess of 90 mm Hg were recorded in areas of colon containing diverticula, and the frequency of contractions producing pressures in excess of 20 mm Hg was quadrupled. Changes occurred within less than 1 min after i.v. morphine, and started about 15 min after i.m. administration. The contractions between different portions of colon were not co-ordinated, and Painter (1963) suggested that segmentation of the bowel was produced by contraction of independent portions, with further contraction of the segments formed. As the contents were not free to escape, high pressures developed within the lumen. While the changes were maximal

in areas of diverticular disease, normal individuals and those who have had an area of diverticular disease excised may be at risk of anastomotic disruption if a colonic anastomosis is subjected to such degrees of pressure.

Ekbom and others (1980) found that contraction forces in the small bowel were increased following administration of morphine in monkeys. Halothane or atropine partially antagonise the effects of morphine on small and large bowel (Marshall, Pittinger and Long, 1961), and naloxone totally reverses it (Kaufman, 1982).

Morphine has been reported to increase splanchnic blood flow by 19% and to decrease splanchnic vascular resistance by 16% (Leaman et al., 1978). However, this study was conducted in patients suffering from chronic heart disease, and changes of this magnitude might not be apparent in normal individuals. Changes in vascular resistance induced by morphine in other vascular beds are reversed by naloxone (Cohen and Coffman, 1980).

Pethidine decreases intraluminal pressure (Painter and Truelove, 1964c) and contraction forces (Ekbom et al., 1980) in the colon. The latter authors noted that small bowel contractility was elevated transiently following i.v. administration of pethidine 1 mg kg^{-1}. Although pethidine may produce constipation because of its actions on the colon, its effect on intracolonic pressure appears to make it in theory a more suitable agent than morphine for treatment of pain following colonic anastomosis.

[2.4.8] Hypocapnia and Hypercapnia

Hypercapnia has been reported to decrease splanchnic blood flow during nitrous oxide anaesthesia, and to increase it during halothane

anaesthesia in man (Epstein et al., 1961; Epstein et al., 1966). The explanation offered was that splanchnic vasoconstriction is produced by the increased sympathetic tone associated with an elevated arterial P_{CO_2}, and while nitrous oxide has no effect upon sympathetic tone, halothane abolishes the increase, allowing the direct vasodilator effect of carbon dioxide to become apparent. However, Hughes and others (1979a) found that portal venous blood flow increased by 16% in response to hypercapnia in dogs anaesthetised with pentobarbitone.

Hypocapnia decreases splanchnic blood flow and increases splanchnic vascular resistance (Johnson, 1975). This appears to be a direct effect of CO_2, and is not simply due to the increase in mean intrathoracic pressure associated with mechanical hyperventilation (Hughes et al., 1979b).

[**2.4.9**] Regional anaesthesia

High spinal nerve block results in increased activity in both small bowel and colon (Burstein, 1939; Garry, 1933), and has been recommended as a therapeutic technique in post-operative ileus (Wilson, 1975). The increased peristaltic activity results from blockade of the sympathetic outflow from the spinal cord, leaving the cranial parasympathetic outflow unopposed. In addition, spinal nerve block reduces plasma catecholamine concentrations to a degree related to the height of block. Plasma adrenaline concentrations are lower during the post-operative period after high spinal anaesthesia than those after general anaesthesia with halothane (Pflug and Halter, 1981).

Whitaker, Dixon and Greatorex (1970) found that the reduction

in canine mesenteric blood flow resulting from haemorrhage could be reversed by sympathetic nerve section. Subarachnoid and extradural anaesthesia result in dilatation of the area of the body caudal to the level of the block (Green et al., 1944). It is therefore possible that the pharmacological sympathectomy associated with these techniques may reduce mesenteric vascular resistance and increase blood flow to the bowel in a similar manner to that resulting from surgical sympathectomy.

[2.5] CONCLUSION

Many factors influence the outcome after surgery of the bowel. However, care in anaesthetic and post-operative management may help to reduce the incidence of complications. In general, factors which improve oxygenation to an anastomosis, and those which minimise increases in contractility may have theoretical benefits.

On reviewing the available literature, it was apparent that three areas of importance required further investigation with regard to the high morbidity and mortality associated with colonic surgery.

1) Regional anaesthesia has a number of theoretical advantages to offer over general anaesthetic techniques, in respect of changes in both contractility and blood flow, and required investigation.

2) Although a number of investigations had been undertaken to study the small bowel, or total mesenteric blood flow, the effects of anaesthetic and surgical factors on blood flow changes in the colon warranted more careful definition because of the influence that blood flow may have on anastomotic healing.

3) The influence of opioid analgesics on anastomotic breakdown required examination because of the differences in effect on bowel contractility between opioid agents.

CHAPTER THREE

A RETROSPECTIVE STUDY OF SPINAL ANAESTHESIA FOR LARGE BOWEL ANASTOMOSIS

[3.1] INTRODUCTION

Subarachnoid and extradural spinal nerve block are known to produce excellent operating conditions in the abdomen, as a result of a combination of profound relaxation of skeletal muscle, minimal haemorrhage and a contracted bowel.

In one surgical unit at the Western Infirmary, Glasgow, it has been for many years the practice of one anaesthetist to use the technique of high spinal nerve block combined with light general anaesthesia in patients undergoing major intra-abdominal surgery. It was the clinical impression of the surgeon that patients undergoing a large bowel anastomosis had a lower incidence of morbidity associated with the anastomosis after operation under spinal nerve block than patients having similar procedures undertaken during conventional general anaesthesia.

High spinal nerve block could theoretically be beneficial in patients undergoing colonic anastomosis because:

1) operative access is improved by the profound skeletal muscle relaxation and contracted bowel
2) reduced bleeding permits easier surgery
3) increased tone in the bowel throughout the procedure may allow easier and safer construction of the anastomosis
4) undesirable effects of neostigmine on the bowel (Painter and

Truelove, 1964b) are avoided.

5) haemodynamic alterations associated with sympathetic blockade may improve blood flow at the anastomotic site.

In order to evaluate the clinical impression of the surgeon, a retrospective study of the outcome of all patients in the unit who had undergone large bowel anastomosis during an 8 yr period was undertaken.

[3.2] PATIENTS AND METHODS

[3.2.1] Patients

Between 1971 and 1975, subarachnoid anaesthesia was employed in 46 patients undergoing large bowel anastomosis (Group A), and between 1968 and 1971, extradural analgesia was used in 30 (Group B). During the period from 1968 to 1975, 30 colonic or rectal anastomoses were constructed under conventional general anaesthesia (Group C). The case records contained sufficient information to permit analysis of 43 operations in Group A, 25 in Group B and 26 in Group C.

[3.2.2] Bowel preparation and anastomosis

In all patients, succinyl sulphathiazole 2.5 g was given orally four times daily for five days, and neomycin sulphate 1.5 g orally four times daily for two days prior to operation, and a bowel washout was performed on the evening before surgery.

All anastomoses were performed by the same surgeon using a two-layer inverting technique, with continuous catgut for the inner layer and interrupted black silk for the outer layer. All were elective procedures.

[3.2.3] Anaesthetic technique

The spinal blocks in patients in Groups A and B were all performed by one anaesthetist, who made no selection of patients for these techniques. The change from extradural to subarachnoid spinal nerve block occurred because of reports (Telivuo and Katz, 1970; Casale, 1970) of systemic toxicity from the large doses of local anaesthetic solution used for high extradural blocks. The patients in Group C were anaesthetised by other anaesthetists. The surgeon did not select any patient for a particular anaesthetist. The choice of anaesthetic technique was determined solely by the anaesthetist in attendance at each operating session.

All patients were premedicated with papaveretum, pethidine, or pethidine and promethazine, and usually with hyoscine or atropine in addition.

Groups A and B

General anaesthesia was induced with i.v. thiopentone, propanidid or Althesin, and endotracheal intubation performed after the administration of suxamethonium. Anaesthesia was maintained with 50% nitrous oxide, supplemented with halothane 0.5%, the patient breathing spontaneously. Spinal nerve block was performed after induction of anaesthesia, with the patient in the lateral position, and the vetebral column horizontal.

Subarachnoid block was performed at the L3-4 or L4-5 interspace using 2.25 - 3 ml cinchocaine 0.5% in 6% dextrose or 1.5 - 1.75 ml amethocaine 1% in an equal volume of 10% glucose. Barbotage was used during injection of the solution. Extradural block was achieved by injecting either 18 - 30 ml of lignocaine 1.5% with adrenaline 1:200,000, or 15 - 20 ml of this solution together with 10 ml of

bupivacaine 0.5% with adrenaline 1:200,000, into the extradural space at L3-4. The intention in all patients was to obtain a sensory block to the fifth thoracic dermatome. Immediately after the block had been performed, the patient was placed supine in a 10 - 15 degree head-down position. This position was maintained for the duration of the operation.

Group C

General anaesthesia was induced with i.v. thiopentone, propanidid or Althesin. Following endotracheal intubation, the lungs were ventilated artificially, and anaesthesia was maintained with 60-70% nitrous oxide in oxygen, supplemented either by halothane or trichloroethylene, or by morphine or papaveretum administered i.v. at induction. Either pancuronium or d-tubocurarine was given i.v., and the effects of the neuromuscular blocking agent were antagonised at the end of the procedure by neostigmine 2.5 mg administered i.v. with atropine 1.2 mg.

Blood loss in all three groups was estimated by weighing the swabs. Arterial pressure was measured in all patients, usually with an oscillotonometer.

[3.2.4] Post-operative analgesia

Analgesia in the post-operative period was provided by i.m. morphine, papaveretum, Cyclimorph or pethidine administered on demand.

[3.2.5] Detection of anastomotic breakdown

Anastomotic disruption was detected clinically using the

following criteria:

1) an escape of flatus and/or faeces to the wound or drain site or to the vagina (Goligher et al., 1970),
2) anastomotic rupture discovered at laparotomy or post mortem, or
3) local abscess formation.

Routine post-operative endoscopy or barium enema were not performed.

[3.2.6] Other factors

1) Post-operative ileus was categorised into that occurring in the first 72 hr after operation, which was likely to be the result of intra-operative handling of the bowel, and that which occurred on or after the fourth post-operative day.
2) The time between operation and the first bowel motion was noted.
3) The duration of intravenous fluid administration and the time of commencing oral fluids were recorded.
4) The nature of opioid analgesics administered before, during and after operation was noted.

[3.2.7] Statistical analysis

Methods applied were Student's t test for unpaired data to test the significance of differences between means of measurements, and the "Four-fold" table and chi-squared tests, with Yates' correction when necessary, for the significance of differences between proportions of observations. Relationships between variables were tested by linear regression analysis using the least squares method.

Differences between the slopes of regression lines were tested for significance using the method described by Petrie (1978). A probability value of less than 0.05 was taken to indicate statistical significance.

[3.3] RESULTS

[3.3.1] Nature of operation

There were no significant differences between the frequencies of each type of operation performed (Table 3.1).

[3.3.2] Pre-operative data

There were no significant differences between the mean ages of patients in the three groups, the values being 63.2 yr (range 20 - 83) in Group A, 66.1 yr (range 39 - 84) in group B, and 63.4 yr (range 26 - 93) in Group C.

The mean haemoglobin concentration was statistically significantly lower in patients in Group A (12.4 $\pm$ 0.3 g dl^{-1}) (mean $\pm$ sem) than in those in Group B (13.7 $\pm$ 0.4) ($p < 0.01$) and Group C (13.4 $\pm$ 0.4) ($p < 0.05$).

[3.3.3] Pathology

Diverticulitis was more common in patients in Group C than in the other two groups (Table 3.2).

[3.3.4] Intra-operative data

The intra-operative data are shown in Table 3.3. Mean operative duration was approximately 1 hr in all groups.

In patients in Group C, there was no consistent trend in

TABLE 3.1 Operations performed. Figures in columns show the number of patients in Groups A (subarachnoid), B (extradural) and C (general anaesthesia), with the percentage of the total (n) in each group in parentheses.

	Anaesthetic group		
	A (n=43)	B (n=25)	C (n=26)
Operation			
Resection of terminal ileum and caecum	4 (9.3)	2 (8.0)	3 (11.5)
Right hemicolectomy	8 (18.6)	7 (28.0)	5 (19.2)
Anastomosis of ileum and transverse colon	1 (2.3)	0 (0)	4 (15.4)
Resection of transverse colon	2 (4.7)	1 (4.0)	1 (3.8)
Left hemicolectomy	5 (11.6)	0 (0)	3 (11.5)
Resection of descending colon	1 (2.3)	0 (0)	0 (0)
Resection of sigmoid colon	10 (23.3)	12 (48.0)	5 (19.2)
Anterior resection of rectum	10 (23.3)	3 (12.0)	2 (7.7)
Rectal polypectomy	2 (4.7)	0 (0)	3 (11.5)

TABLE 3.2 Distribution of pathology in Groups A (subarachnoid), B (extradural) and C (general anaesthesia). Figures in columns show the number of patients, with the percentage of the group total (n) in parentheses.

	Anaesthetic group		
	A (n=43)	B (n=25)	C (n=26)
Pathology			
Carcinoma	28 (65.1)	14 (56.0)	15 (57.7)
Crohn's disease	8 (18.6)	1 (4.0)	5 (19.2)
Diverticulitis	2*(4.7)	10*(40.0)	0*(0)
Rectal polyp	2 (4.7)	0 (0)	3 (11.5)
Other+	3 (7.0)	0 (0)	3 (11.5)

+One case of tuberculosis. All other cases either inflammatory, or mechanical obstruction.

*A v. B and C v. B - $p < 0.01$

TABLE 3.3 Intra-operative data for patients in Groups A (sub-arachnoid), B (extradural) and C (general anaesthesia). N.A. denotes that values were not available.

	Anaesthetic group		
	A (n=43)	B (n=25)	C (n=26)
	Mean (sem)	**Mean (sem)**	**Mean (sem)**
Operative duration (min)	57.3 (2.0)	56.6 (3.0)	63.0 (5.0)
Pre-operative mean arterial pressure (mm Hg)	102 (4)	109 (3)	N.A.
Minimum intra-operative mean arterial pressure (mm Hg)	42 (1)	43 (2)	N.A.
Decrease in mean arterial pressure (%)	58.5 (1.4)	59.6 (2.3)	N.A.

intra-operative arterial pressure. In Groups A and B, arterial hypotension occurred in all patients shortly after spinal block had been performed, and persisted into the early post-operative period. There were no significant differences between pre-operative mean arterial pressure, minimum intra-operative mean arterial pressure, or percentage decrease in mean arterial pressure. Within each of the two groups, there was a linear relationship between pre-operative mean arterial pressure and the percentage decrease in arterial pressure to the minimum intra-operative value (Figure 3.1).

Mean intra-operative blood loss (Figure 3.2) in Group C (430 ± 109 ml) was more than ten times greater than that in Group A (27 ± 4 ml) or Group B (42 ± 14 ml). Eight patients in Group C required intra-operative blood transfusion. No patients in Groups A or B required blood transfusion intra- or post-operatively.

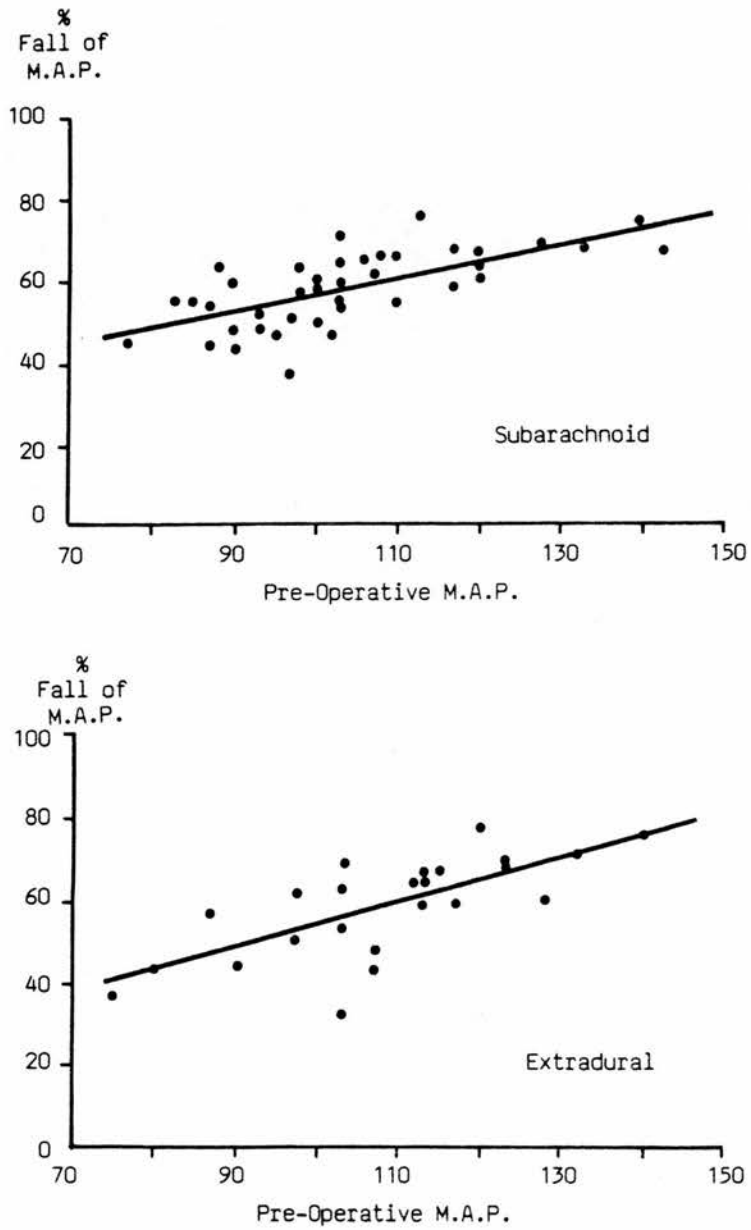
[3.3.5] Post-operative fluids

The mean duration of intravenous fluid administration was significantly shorter in Group B than in the other groups (Table 3.4). There were no significant differences between groups in respect of the period between operation and the time at which oral fluids were started.

[3.3.6] Other post-operative data

The occurrence of post-operative mechanical or paralytic ileus (Figure 3.3) appeared more common in patients in Group C (early 19.2%, late 23.1%) than in Group A (early 11.6%, late 11.6%) or Group B (early 12%, late 4%), but the differences were not statistically significant.

FIGURE 3.1

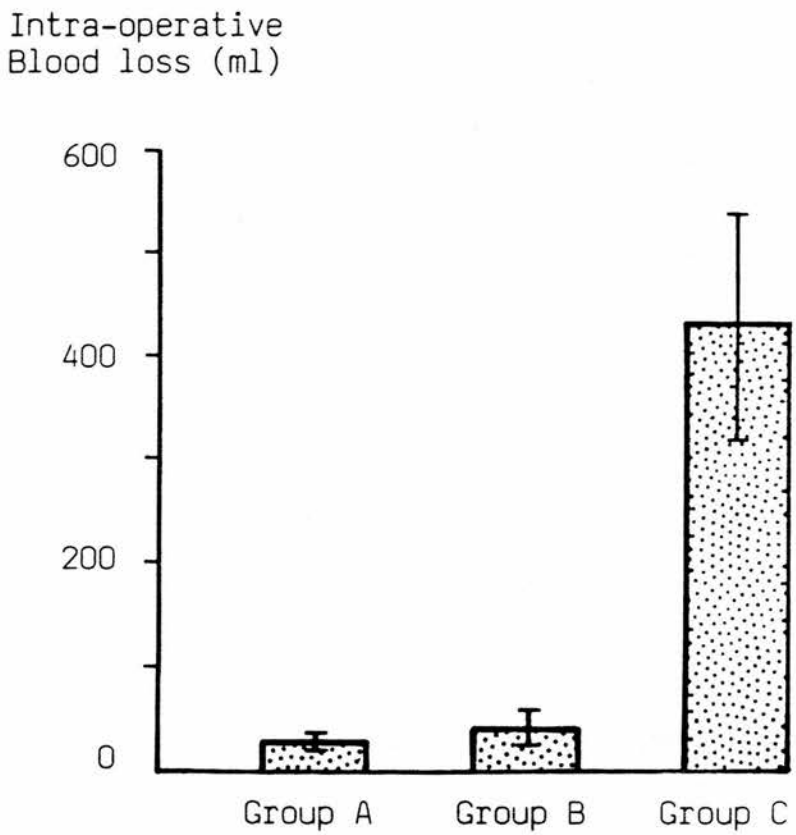


Relationship between pre-operative mean arterial pressure (M.A.P.) and percentage decrease in mean arterial pressure to the minimum intra-operative value in 43 patients (Group A) who received subarachnoid spinal nerve block and 25 patients (Group B) who received extradural spinal nerve block for colonic resection. The regression line equations are:

Subarachnoid; $y = 0.403x + 16.63$ $r = 0.675$ $p < 0.001$

Extradural; $y = 0.556x - 1.096$ $r = 0.674$ $p < 0.001$

No significant difference between slopes



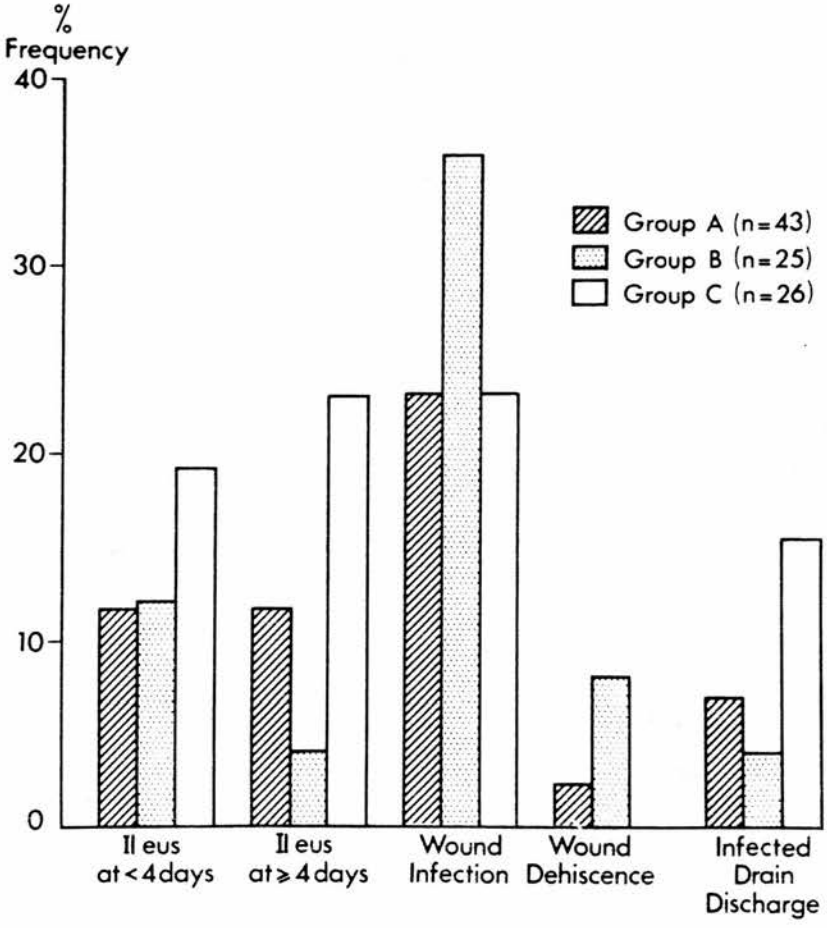
Comparison of intra-operative blood loss in the three anaesthetic groups. Blocks represent the mean values (bars represent sem) from 43 patients in Group A (subarachnoid), 25 patients in Group B (extra-dural) and 26 patients in Group C (general anaesthesia). Group A v. Group C; $p < 0.001$. Group B v. Group C; $p < 0.001$.

TABLE 3.4 Timing of commencement of oral fluids and discontinuation of intravenous fluid for patients in Groups A (subarachnoid), B (extradural) and C (general anaesthesia).

	Anaesthetic group		
	A (n=43)	B (n=25)	C (n=26)
	Mean (sem)	**Mean (sem)**	**Mean (sem)**
Oral fluids started (hr post-op)	33.1 (2.2)	27.7 (2.4)	32.4 (3.2)
Intravenous fluids stopped (hr post-op)	57.7*(3.6)	40.3*(3.4)	57.7*(4.6)

*A v. B and C v. B - $p < 0.01$

FIGURE 3.3



Incidences expressed as percentage of group total (n) of post-operative complications related to the abdomen in patients in Groups A (subarachnoid), B (extradural) and C (general anaesthesia. No significant differences.

The frequencies of wound and drain complications in the three groups were not significantly different. The frequency of wound infection was high in all groups.

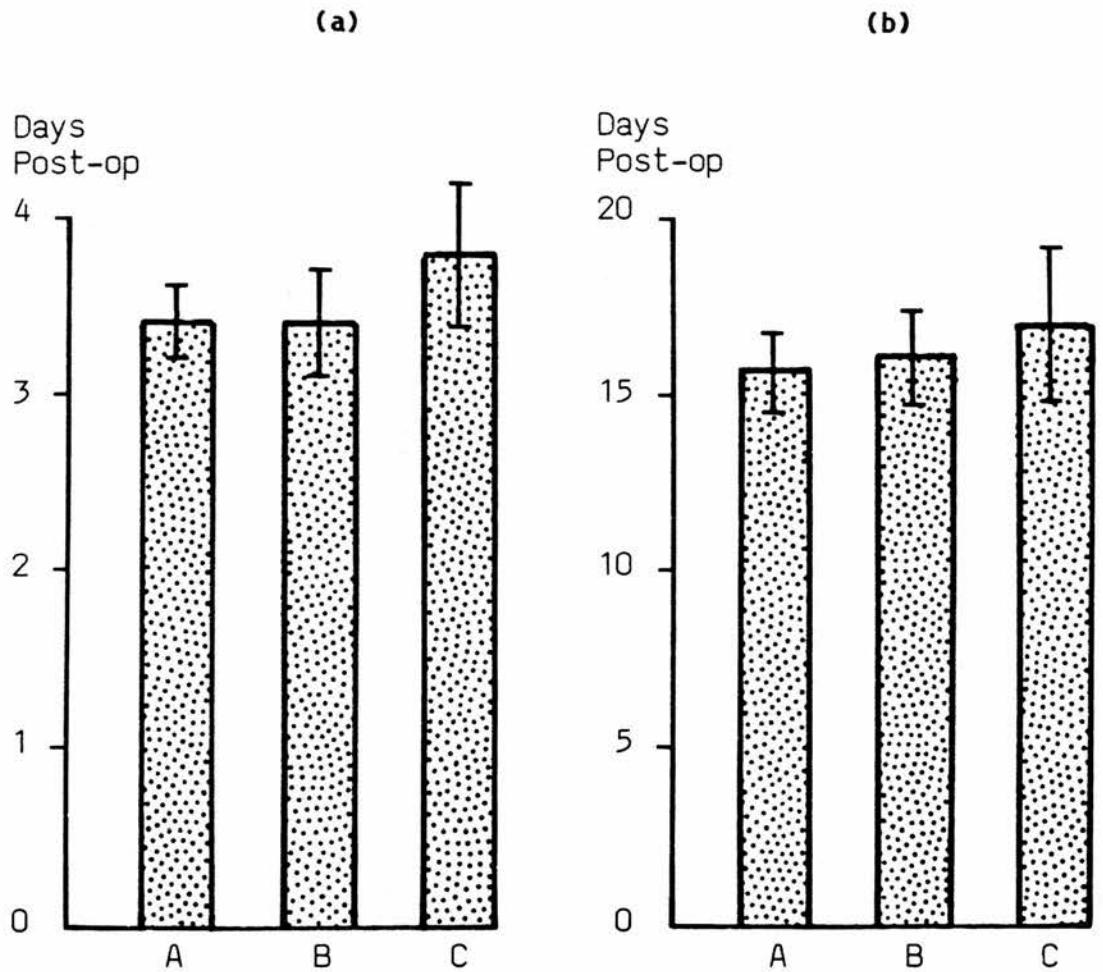
There were no significant differences between the groups with regard to time to first bowel motion, or duration of hospital stay (Figure 3.4). The mean duration of stay in hospital was 15.7 days in Group A, 16.1 days in Group B, and 17.0 days in Group C.

[3.3.7] Anastomotic breakdown

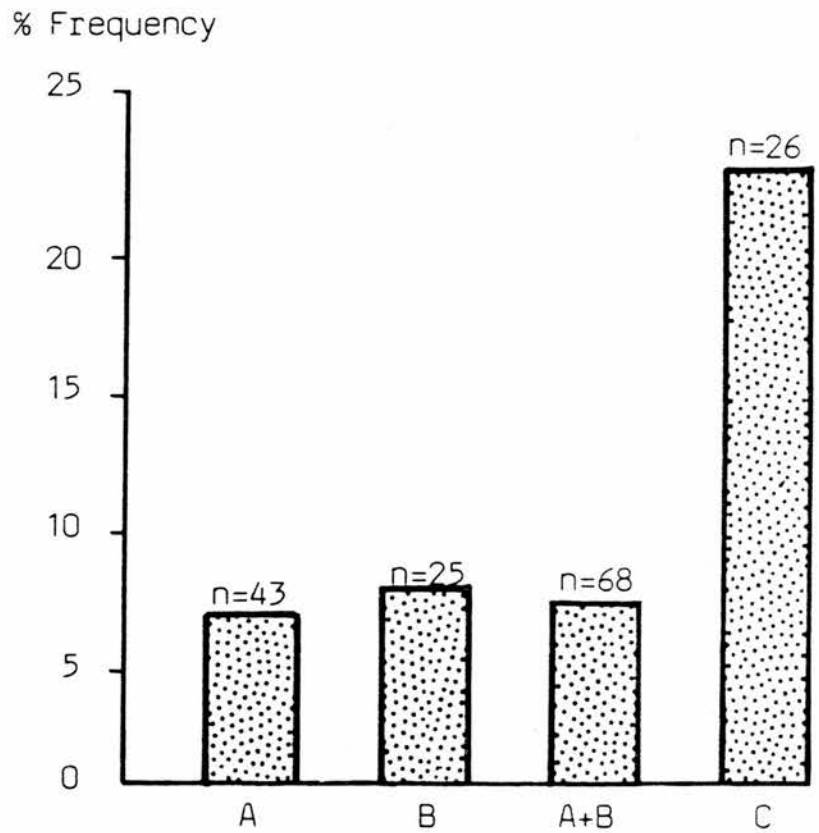
The frequencies of anastomotic breakdown are shown in Figure 3.5. Three patients in Group A (7.0%) and two in Group B (8.0%) suffered dehiscence of the anastomosis, compared with six patients in Group C (23.1%). However, these differences do not achieve statistical significance at the 5% level.

[3.3.8] Opioid administration

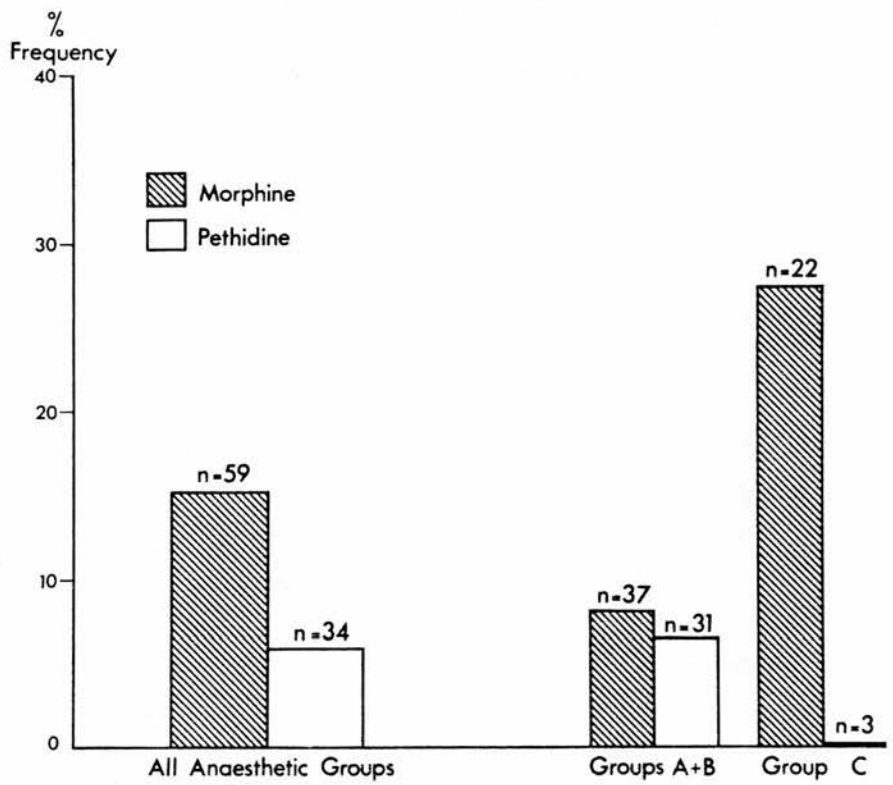
Figure 3.6 shows the frequency of anastomotic breakdown in relation to the administration of morphine (or drugs containing morphine) and pethidine before, during and after operation. The group totals in this Figure represent patients who received only one type of opioid throughout the peri-operative period, i.e. patients who received both have been excluded. The frequency of anastomotic disruption appeared to be greater in association with the administration of morphine, irrespective of the method of anaesthesia employed. Considering all patients, 15.2% of those who received morphine suffered an anastomotic breakdown compared with 5.9% of those who received pethidine. In patients who received spinal nerve block (Groups A and B) the frequency of anastomotic disruption associated with the



(a) Mean time to passage of the first bowel motion after operation, and (b) mean duration of stay in hospital following colonic anastomosis. Bars represent sem. Group A (subarachnoid, 43 patients); Group B (extradural, 25 patients); Group C (general anaesthesia, 26 patients).



Incidence of anastomotic breakdown in relation to anaesthetic technique. Values from Groups A (subarachnoid), B (extradural), A and B combined (all spinal nerve block) and C (general anaesthesia) are expressed as the percentage frequency of the group total (n).



Incidence of anastomotic breakdown in relation to administration of opioid analgesics. Values are expressed as the percentage frequency of the group total (n) for (left) all patients, and (right) patients who received spinal nerve block (Groups A and B) or general anaesthesia (Group C).

use of morphine (8.1%) appeared less than that in the patients in Group C who received morphine (27.3%). However, none of these apparent differences was statistically significant.

[3.3.9] Mortality

The mortality rates and causes of death are listed in Table 3.5. There were no significant differences between groups. An autopsy was performed on all patients who died. Three of the seven deaths were associated with anastomotic breakdown.

[3.3.10] Patients with anastomotic breakdown

Data from patients whose anastomosis dehisced was compared with that from all other patients irrespective of the method of anaesthesia employed. The incidence of anastomotic breakdown was highest in patients who had undergone anterior resection of the rectum (Table 3.6). There was no obvious influence of age, pre-operative haemoglobin concentration, operative duration, or minimum intra-operative arterial pressure on the outcome of the procedure (Table 3.7). The time of starting oral fluids, duration of intravenous fluid administration, and time of first bowel motion were not significantly different between groups. As might be expected, patients whose anastomosis dehisced remained longer in hospital.

In those patients whose anastomosis broke down, higher frequencies were recorded of ileus and wound infection (Table 3.8), although these did not achieve statistical significance. An infected drain site was significantly commoner in patients with anastomotic breakdown than in the other patients. There was a highly significant difference between groups in respect of the proportion of patients

TABLE 3.5 Mortality in Groups A (subarachnoid), B (extradural) and C (general anaesthesia).

Anaesthetic group	No. of patients	% of group total	Cause of death confirmed by post-mortem
A (n = 43)	1	2.3	Myocardial infarction 17th day
B (n = 25)	3	12.0	Myocardial infarction 8 hr post-op; infarction was 36 hr old Peritonitis following anastomotic break-down 5th day Bronchopneumonia 19th day
C (n = 26)	3	11.5	Massive pulmonary embolism 4th day Haemorrhage from anastomosis and myocardial infarction 2nd day Peritonitis following anastomotic break-down 20th day

No significant differences between groups.

TABLE 3.6 Nature of operation and pathology in patients whose anastomosis broke down compared with other patients. Figures in columns show the number of patients, with the percentage of the total (n) in each group in parentheses.

	Anastomotic fate	
	Broke down (n = 11)	Remained intact (n = 83)
Operation		
Resection of terminal ileum and caecum	1 (9.1)	8 (9.6)
Right hemicolectomy	2 (18.2)	18 (21.7)
Anastomosis of ileum and transverse colon	0 (0)	5 (6.0)
Resection of transverse colon	1 (9.1)	3 (3.6)
Left hemicolectomy	0 (0)	8 (9.6)
Resection of descending colon	1 (9.1)	0 (0)
Resection of sigmoid colon	1 (9.1)	26 (31.3)
Anterior resection of rectum	4 (36.4)	11 (13.3)
Rectal polypectomy	1 (9.1)	4 (4.8)
Pathology		
Carcinoma	7 (63.6)	50 (60.2)
Crohn's disease	2 (18.2)	12 (14.5)
Diverticulitis	1 (9.1)	11 (13.3)
Rectal polyp	1 (9.1)	4 (4.8)
Other	0 (0)	6 (7.2)

No significant differences

TABLE 3.7 Additional data for patients whose anastomosis broke down compared with other patients.

	Anastomotic fate			
	Broke down (n_1= 11)		Remained intact (n_2= 83)	
	mean	**sem**	**mean**	**sem**
Age (years)	69.2	3.0	63.3	1.7
Haemoglobin (g dl^{-1})	13.6	0.7	13.0	0.2
Duration of operation (min)	57.1	3.1	57.5	1.7
Minimum intra-op. mean arterial pressure (mm Hg)[+]	41	4	43	1
Oral fluids started (hr after operation)	36.0	5.4	31.0	1.5
I.v. fluids stopped (hr after operation)	61.3	8.8	52.4	2.5
Hospital stay (days after operation)	23.3*	3.4	15.5*	0.9

*$p < 0.05$

[+]Data for groups A and B only (n_1= 5; n_2= 63)

TABLE 3.7

TABLE 3.8 Additional data for patients whose anastomosis broke down compared with other patients.

	Anastomotic fate			
	Broke down (n = 11)		Remained intact (n = 83)	
	No. of patients	% group total	No. of patients	% group total
Early ileus	2	18.2	11	13.3
Late ileus	4	36.4	8	9.6
Wound infection	6	54.5	19	22.9
Wound dehiscence	0	0	3	3.6
Drain discharge	5^{+}	45.5	3^{+}	3.6
Death	4^{*}	36.4	3^{*}	3.6
Morphine	9	81.8	50	60.2
Pethidine	2	18.2	32	38.6

$^{*}p < 0.05$ $^{+}p < 0.01$

who died.

Although a higher proportion of the patients whose anastomosis broke down had received morphine than patients whose anastomosis remained intact, this difference was not statistically significant.

[3.4] DISCUSSION

Although the differences between the groups did not attain statistical significance, the higher frequency of anastomotic breakdown in Group C compared with the subarachnoid or extradural groups, together with a higher frequency of post-operative ileus, suggests that spinal nerve block may have exerted some beneficial effect on large bowel anastomoses, since other factors were similar in the three groups.

Among the factors thought to be associated with an increased frequency of anastomotic dehiscence are increasing age, a pre-operative haematocrit of less than 35%, the presence of peritonitis, blood transfusion, increasing operative duration, rectal anastomoses, low plasma protein concentrations, and resections of tumours which have metastasised or are adherent to other structures (Schrock, Deveney and Dunphy, 1973; Irvin and Goligher, 1973). Findings have varied as to whether elective procedures have a significantly lower breakdown rate than emergency operations.

All operations in the present study were elective procedures. The ages of the patients were similar in all groups, and none had pre-operative anaemia. The operative duration was about 1 hr in all groups, and the frequency of rectal anastomosis was highest in Group A (subarachnoid block), which had the lowest frequency of anastomotic breakdown.

If a beneficial effect from spinal nerve block does exist, it may be a result of improved operating conditions, decreased haemorrhage, an effect on blood flow at the anastomotic site, the avoidance of neostigmine, or any combination of these factors.

Spinal nerve block produces sympathetic denervation of the small and large bowel. The small bowel and right hemicolon receive their parasympathetic innervation from the vagus nerve, which is not involved in spinal nerve block, and the effects of the sympathetic block are an increase in the propulsive force of peristalsis, and an increase in intraluminal pressure (Greene, 1981). The left hemicolon receives its parasympathetic innervation from the sacral roots, and so both sympathetic and parasympathetic denervation occur with spinal nerve block. However, the net effect is an increase in bowel tone. This might result in better construction of the anastomosis, or less marked changes in intracolonic pressures in the period immediately after anaesthesia. Shaw and Wolcott (1963) reported that flatus was passed earlier after operations undertaken during spinal anaesthesia than after similar procedures carried out under general anaesthesia. After colonic surgery, such an effect may minimise gaseous distension leading to a gas leak at the anastomosis, which could result subsequently in anastomotic breakdown. Treissman (1980) reported two cases of early disruption of colonic anastomosis associated with extradural anaesthesia, and concluded that colonic surgery was a relative contra-indication to the use of spinal nerve block. This conclusion was based on the assumption that removal of sympathetic activity to the intestine may cause strong contractions in the colon and strain the suture line. However, Bigler, Hjortsø and Kehlet (1985), in reporting a similar case, concluded that it was unlikely that extradural

anaesthesia produced anastomotic breakdown, but that it might permit earlier detection and treatment of a disruption due to other causes by preventing the normal post-operative colonic atony.

The duration of intravenous fluid administration and the delay in starting oral fluids may be an indication of disordered bowel activity and anastomotic dysfunction. The mean values of both appeared to be shorter in patients receiving an extradural block (Group B) than in other patients. However patients given an extradural block were all operated upon in the earlier part of the period studied. Separate analysis of data from patients in Group C for the earlier and later parts of the study suggests that a more conservative approach to early oral feeding developed during the course of the period studied, and that this was responsible for the apparent differences between groups .

In a series of 650 cases of anterior resection of rectum or left hemicolectomy, Whitaker, Dixon and Greatorex (1970) found that the frequency of anastomotic dehiscence, which averaged 16.1%, was proportional to the volume of blood transfused during operation. In experiments on dogs in which 10% of blood volume was removed, they found a large decrease in mesenteric blood flow, which was not always reversed by reinfusion of the shed blood. They concluded that the anastomotic leakage rate in their human series was probably related to blood loss rather than blood transfusion. They also found that sympathetic nerve section in the retransfused dogs resulted in restoration of normal mesenteric blood flow.

In the present study, the mean blood loss was very much less in patients in Groups A and B than in Group C. The small blood loss during spinal nerve block is probably the result of a combination of

decreased local arterial and venous pressures as a consequence of arterial hypotension, venous dilatation and posture (Moir, 1968).

High spinal nerve block produces dilatation of resistance and capacitance vessels by blocking the sympathetic nerve supply to the affected segments. Normovolaemic, unanaesthetised subjects are able to compensate for the vasodilatation by reflex vasoconstriction in the upper part of the body, resulting in a small decrease (5 - 16%) in mean arterial pressure and a small increase in heart rate from stimulation of cardiac sympathetic fibres above T5 (McLean et al., 1967). The vasoconstrictive compensatory mechanism is abolished, at least in part, in anaesthetised subjects. Defalque (1962) demonstrated that the degree of hypotension was linearly related to the height of block, and that a greater decrease in arterial pressure was associated with extradural blocks. The latter finding was not confirmed by Ward and others (1965). Blocks above T5 reduce cardiac rate and stroke volume, resulting in decreases in cardiac output and arterial pressure (McLean et al., 1967).

The effects of adrenaline in extradural anaesthetic solutions are mainly those of ß-adrenergic stimulation because the total dose administered is small (Stanton-Hicks, 1975). There is thus an increase in heart rate and stroke volume, but a decrease in systemic vascular resistance as a result of arteriolar dilatation in skeletal muscle. The net result is a small decrease in arterial pressure. The systemic effects on the cardiovascular system of local anaesthetic agents may result in an increase or decrease in cardiac output and arterial pressure, depending on the concentration in blood.

Ward and his colleagues (1965), who performed either subarachnoid or extradural spinal nerve block on unanaesthetised subjects to

attain a sensory block to T5 (which would produce a sympathetic block about two segments higher in the subjects receiving subarachnoid block) found almost no difference in arterial pressure decrease between extradural block with solutions containing adrenaline (22%) and subarachnoid block (21.3%). When extradural block was performed without adrenaline, arterial pressure decreased by only 8.9%. However, alterations in cardiac output differed widely, decreasing by 18% after subarachnoid block, increasing by 30% after extradural block with adrenaline-containing solutions, and decreasing by 5% after extradural block without adrenaline, thus demonstrating the marked differences in systemic vascular resistance which occur to produce the observed effects on arterial pressure.

In the present study, adrenaline was present in all local anaesthetic solutions used for extradural block. The mean percentage decrease in mean arterial pressure from pre-operative to minimum intra-operative values was similar in Group A (58.5%) and Group B (59.6%). These decreases were large partly because the patients were anaesthetised. Kleinerman, Sancetta and Hackel (1958) found that decreases in arterial pressure associated with spinal nerve block were greater in hypertensive than in normotensive patients. This was confirmed in the present study.

The percentage reduction in mean arterial pressure was similar in patients whose anastomosis dehisced (60.8%) and other patients (58.8%) when only patients who received spinal nerve block were considered. Schrock, Deveney and Dunphy (1973) found that the anastomotic breakdown rate almost doubled in patients who were hypotensive (defined by them as a systolic arterial pressure decrease of 50 mm Hg below baseline for 15 min or longer) during operation, but their

patients were almost certainly hypotensive as a result of haemorrhage. The findings in the present study do not suggest that hypotension associated with vasodilatation has a deleterious effect on bowel anastomoses.

Neostigmine is known to increase contractility in the bowel (Bárány and Jacobson, 1964), particularly in patients with diverticular disease (Painter and Truelove, 1964b). Whitaker (1968) found that inferior mesenteric artery flow was reduced by the administration of neostigmine to dogs. However, cardiac output also decreased in response to neostigmine in two of the three dogs in which it was measured. Atropine given to dogs prior to the administration of neostigmine protected against the reduction of blood flow in most animals, and atropine given after neostigmine restored mesenteric blood flow to at least control values. Prior administration of atropine or glycopyrronium does not abolish the increase in intraluminal pressure caused by neostigmine in conscious subjects (Child, 1984).

Bell and Lewis (1968) reported that the incidence of anastomotic breakdown in patients undergoing ileorectal anastomosis was significantly higher in those who received neostigmine than those who did not. However, subsequent investigations by Wilkins and others (1970) demonstrated that although neostigmine has a pronounced effect on the contractility of the ileum, only 20% of patients anaesthetised with nitrous oxide showed any colonic response to the drug. Halothane abolished the response to neostigmine in colon and rectum, and reduced it considerably in the ileum. In addition, Whitaker (1968) could find no correlation between dose of neostigmine and anastomotic breakdown rate in an analysis of the records of 144 patients.

In the present study, all patients received atropine at the same time as neostigmine. The proportion of patients undergoing an anastomosis involving the ileum (resection of terminal ileum and caecum, or right hemicolectomy) was virtually identical in the patients whose anastomosis broke down to the proportion in the other patients. In addition, most of the patients in Group C received halothane. Thus, it seems unlikely that the administration of neostigmine had a significant influence on the outcome of the anastomosis.

Morphine has been shown to induce strong contractions of the colon in a non-peristaltic manner (Painter and Truelove, 1964a). As with neostigmine, the pressure changes are maximal in patients with diverticular disease, but an increased frequency of contractions resulting in intraluminal pressures of up to 50 mm Hg was recorded in normal individuals. However, morphine has a direct action on the colon, and so, unlike neostigmine, it will produce increased contractility even in a denervated segment. Although halothane antagonises the effect of morphine on the colon, morphine is often administered for 48 - 96 hr post-operatively in addition to its use as a supplement during general anaesthesia, and may thus induce increased intracolonic pressures over a prolonged period before an anastomosis has healed securely.

The primary purpose of the present study was not to investigate the effects of morphine and pethidine. The decision to prescribe morphine or pethidine in the post-operative period was made by several anaesthetists, and may have been based upon the general condition of the patient. Nevertheless, irrespective of the criteria used to group patients for analysis of the effects of opioid drugs, there appeared to be a trend suggesting that patients who received

morphine had a higher incidence of anastomotic disruption. This subject appears to warrant further investigation.

This study has the disadvantage of being retrospective, with the result that the conditions of the investigation were not controlled rigidly. Surgical technique, faecal spillage, the appearance of the bowel and many other factors cannot be assessed adequately. In addition, the number of patients studied was small. It is difficult in any one hospital to obtain data in a reasonable period of time on a large number of patients undergoing large bowel anastomosis. Nevertheless, the findings suggested that subarachnoid and extradural anaesthesia might offer some protection following colonic anastomosis, and that further investigation of the effects of spinal nerve block on the colon were warranted.

CHAPTER FOUR

AN ANIMAL MODEL FOR MEASUREMENT OF COLONIC BLOOD FLOW AND OXYGEN CONSUMPTION

[4.1] INTRODUCTION

Clearly, detailed investigation of the effects of anaesthetic and surgical factors on colonic haemodynamics cannot be undertaken using human subjects. It was therefore appropriate to consider the development of an animal model in which colonic blood flow could be measured accurately and reproducibly. Although previous studies had been undertaken to measure colon blood flow (Hultén et al., 1976a; Bacaner, 1966; Welsh, 1963; Hanson and Moore, 1969), the authors had used techniques which were relatively insensitive or had interfered substantially with the integrity of the colon itself, its blood supply or its nerve supply. In addition, none of these studies attempted to measure oxygen delivery to, or consumption by, the colon.

In designing an animal model, it was desirable that the anatomy of the abdominal contents should be related as closely as possible to that of man. In addition, a large animal was necessary in order that blood flow could be measured with the minimum disturbance to the normal anatomy, and so that relatively large volumes of blood could be sampled for biochemical analysis. Ideally, a large primate would have been selected. However, because of the number of experiments anticipated, the use of primates was impractical. Although the anatomy of the canine colon differs to some degree from that of the

human, it appears to be similar in most respects to the human left hemicolon. In addition, the scale is appropriate if large breeds of dog are used. Access was available to adequate numbers of a single breed (the greyhound), and as a result of all these considerations, a dog model was selected.

This chapter describes in detail the methodology relevant to the series of experiments described in the ensuing chapters. Once established, the same basic model was used in all subsequent experiments, although each series of experiments involving specific physiological or pharmacological manoeuvres necessitated individual modifications to the standard protocol. These modifications are described in the appropriate chapters. Some experiments were performed with the sole purpose of validating the model, particularly in respect of the method of measuring colon blood flow, and these are dealt with in this chapter. Although some of the previously well established techniques which were used are mentioned, with appropriate references, emphasis in this chapter has been placed on new methods developed during these experiments. Theoretical considerations relevant to the method of blood flow measurement are dealt with in the discussion section.

[4.2] EXPERIMENTAL METHODS

[4.2.1] The dog model

Experiments were performed on adult greyhound dogs of either sex weighing between 20 and 35 kg (mean 26.4 kg, standard deviation 3.6 kg). General anaesthesia was induced with pentobarbitone 30 - 40 mg kg^{-1} injected intravenously into the left cephalic vein. The animal was positioned on the operating table in the right lateral

position, and the trachea was intubated. Neuromuscular blockade was induced with pancuronium 0.1 mg kg^{-1}, and intermittent positive pressure ventilation of the lungs instituted using a Palmer respiratory pump. Respiratory rate was maintained in all experiments at 14 breath min^{-1}. Gas from the catheter mount of the endotracheal tube was sampled continuously for measurement of carbon dioxide concentration by an infra-red analyser. The tidal volume of the Palmer pump was adjusted to maintain an end-tidal carbon dioxide concentration of approximately 5%. Following insertion of an intra-arterial catheter (vide infra), tidal volume was adjusted to maintain an arterial carbon dioxide tension (P_aCO_2) between 4.9 and 5.7 kPa. The inspired gas consisted of a mixture of oxygen and nitrogen delivered from cylinders and regulated by rotameters. The proportions of these gases were adjusted to produce an arterial oxygen tension (P_aO_2) of 12.0 - 16.0 kPa. Anaesthesia was maintained with supplements of pentobarbitone 5 mg kg^{-1} administered intravenously as required, usually every 90 - 120 min. Pancuronium 0.05 mg kg^{-1} was administered with each supplement of pentobarbitone.

The expired gases were vented to the outside atmosphere via a length of plastic tubing led out through the laboratory window.

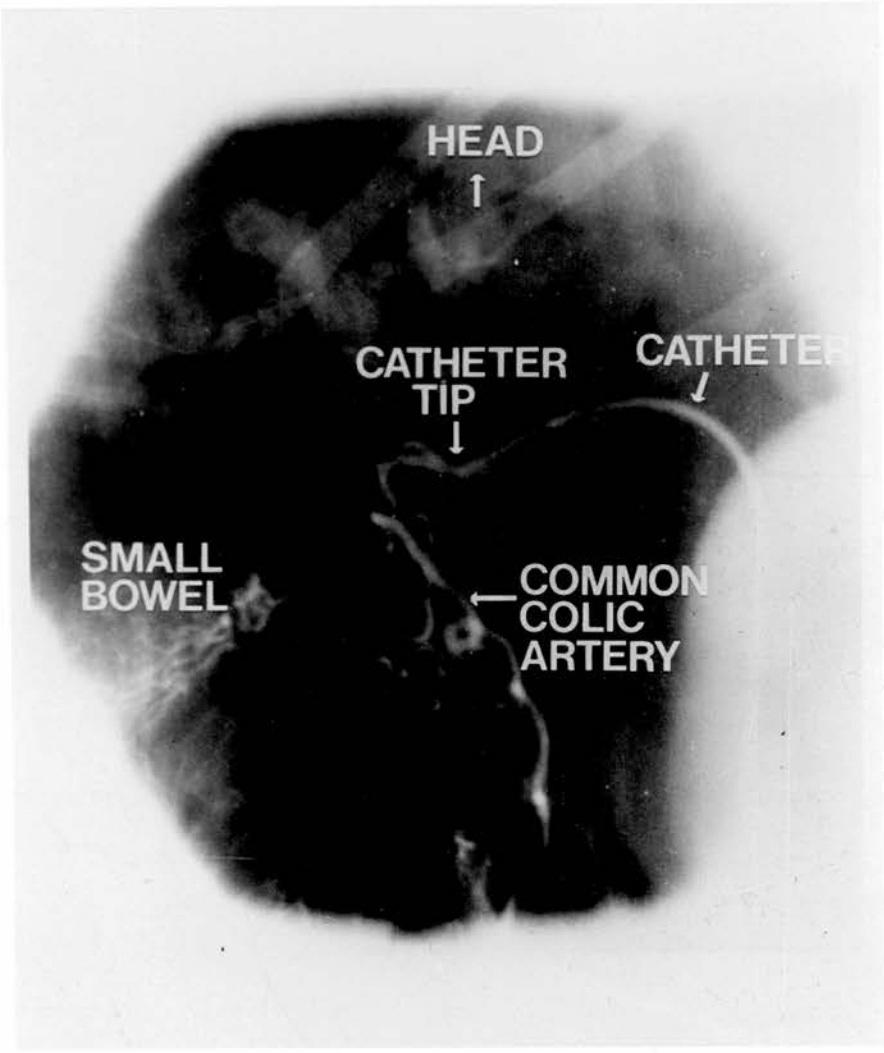
An intravenous infusion was established via the left cephalic vein and a solution of sodium chloride 0.9% was infused at a rate of 5 ml kg^{-1} hr^{-1} in an attempt to maintain adequate hydration and electrolyte balance during the experiment. A pulmonary artery catheter was introduced into the left jugular vein and advanced under x-ray control using an image intensifier system until its tip lay in the proximal pulmonary artery. 14 gauge polythene catheters were inserted into the left femoral vein and artery and positioned such that their

tips lay in the right atrium and in the descending aorta respectively. All three catheters were connected to pressure transducers (Elema-Schonander EMT 33 and 35) whose signals were displayed on an eight channel ink-jet recorder (Elema-Schonander Mingograf 81) together with the electrocardiograph (ECG) recorded from leads inserted subcutaneously in each limb. Thus heart rate, systemic arterial pressure, pulmonary arterial pressure and right atrial pressure could be monitored continuously.

Cardiac output was measured by the thermal dilution technique using the pulmonary artery catheter and a cardiac output computer (Cardiovascular Instruments Type 3750) (Douglas et al., 1975). Core temperature was measured from the mid-oesophagus using a direct recording thermocouple.

After placement of the monitoring catheters, the abdomen was opened through a midline incision and splenectomy performed. A number 4 Cournand cardiac catheter was then introduced via the right femoral artery and manoeuvred under x-ray control until its tip lay in the cranial mesenteric artery just proximal to the common colic artery, which was invariably the first large branch (Figure 4.1). A 20 gauge Teflon cannula (Cathlon™, Critikon Inc.) was introduced through a small mesenteric vein draining from the colon, and advanced until its tip lay in the main marginal vein of the colon (Figure 4.2). The cannula was secured in place by suturing to the mesentery and connected to a three-way tap via an extension catheter which was brought out through the caudal end of the wound (Figure 4.3). Colonic venous blood samples could thus be obtained easily. The colonic loop was then approximated to the abdominal wall in a natural position to the left of the midline using two silk sutures 3 cm apart passed through

FIGURE 4.1



Lateral radiograph of a dog abdomen demonstrating the distribution of radio-opaque dye following injection through the catheter positioned in the cranial mesenteric artery. Dye is distributed along the cranial mesenteric artery to the small bowel, and along the common colic artery to the colon. The opacity at the lower right border is the kidney, which had concentrated dye injected previously in attempts to obtain satisfactory photographs. Normally, only a small volume of dye was used to confirm the position of the catheter.

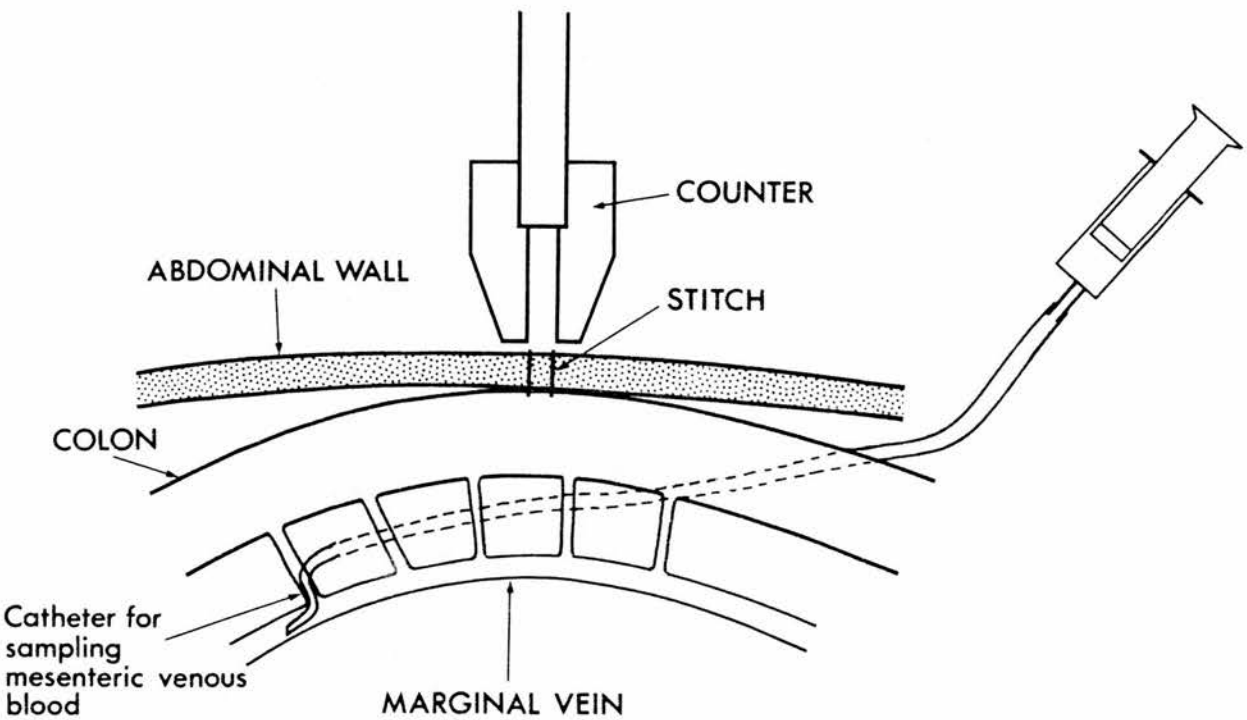
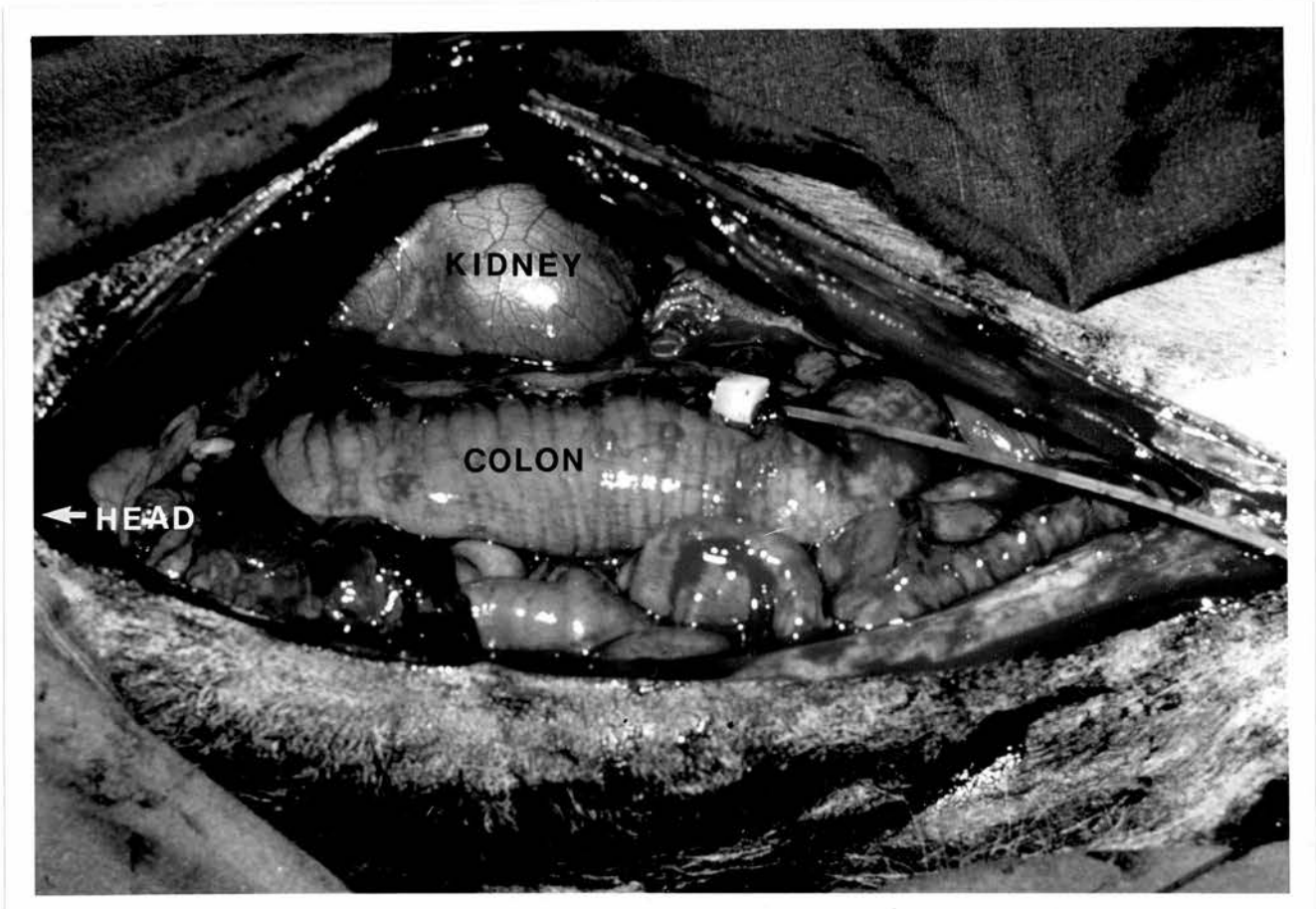


Diagram in longitudinal section demonstrating the position of the catheter inserted into a small mesenteric vein and advanced into the marginal vein of the colon. The antimesenteric border of the colon was later sutured to the anterior abdominal wall and a scintillation counter positioned over the sutures.



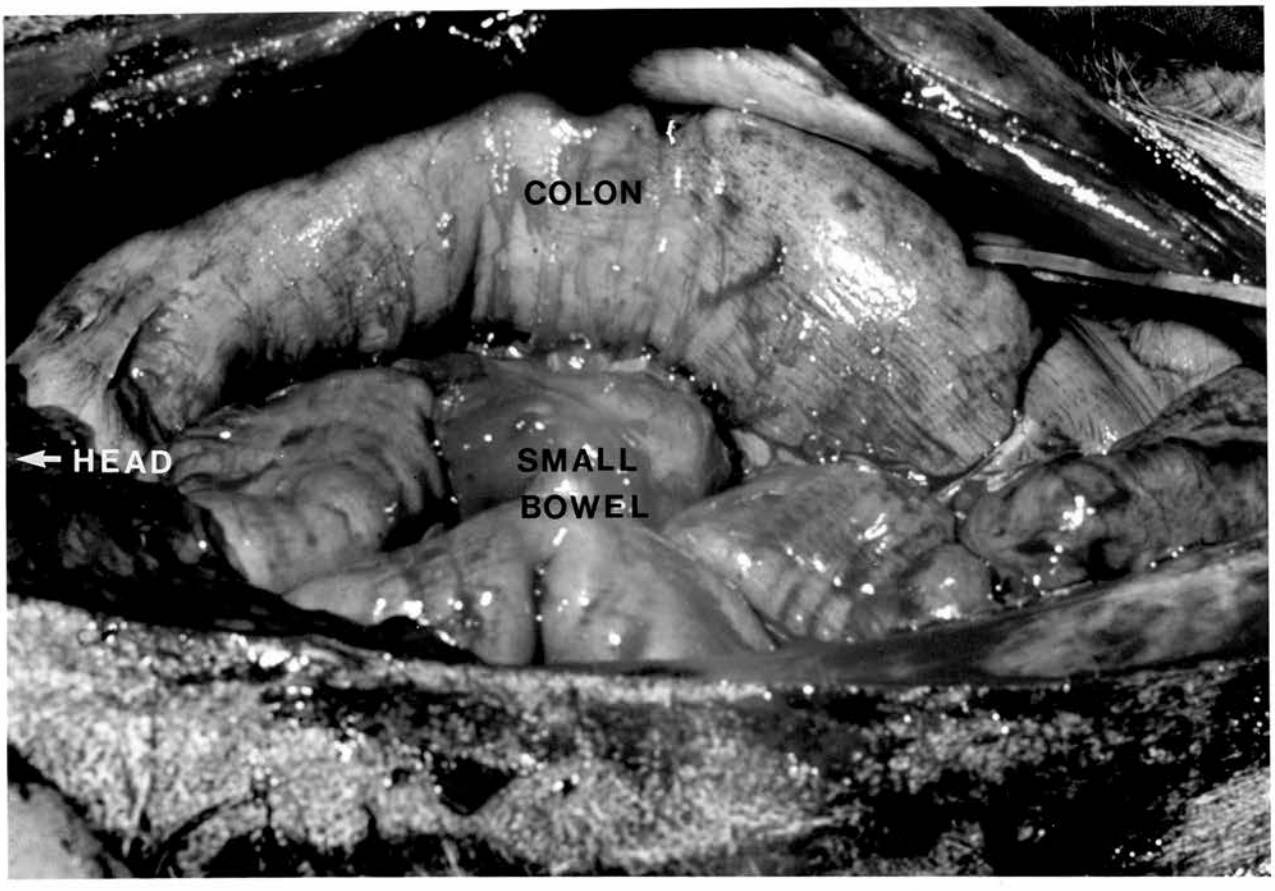
Photograph of a dog abdomen during laparotomy, showing the position of the colonic mesenteric catheter after insertion. The catheter is held in place by a suture and is connected to polythene tubing sutured gently to the colon.

the abdominal wall (Figure 4.4). The small bowel was lightly packed off to the right side of the abdomen (where it fell naturally) and the wound was then closed with through and through silk sutures.

A collimated scintillation counter was positioned over the dog at an angle of 45 degrees (Figure 4.5) using as markers the two silk sutures securing the colon in position. The counter thus pointed directly at the loop of the colon, with the small bowel lying outside its field of uptake (Figure 4.6). Colon blood flow was measured using a radioactive isotope washout technique. A bolus of xenon-133 (500 μCi) dissolved in 0.3 - 1 ml of sodium chloride 0.9% (the volume varied with the age of the isotope), followed by 4 ml sodium chloride 0.9%, was injected through the mesenteric artery catheter, the complete injection sequence lasting 3 sec. The washout of gamma activity from the colon was recorded using a ratemeter and potentiometric pen recorder (Servoscribe) and the colon blood flow calculated from the first 90 sec of the washout curve (vide infra).

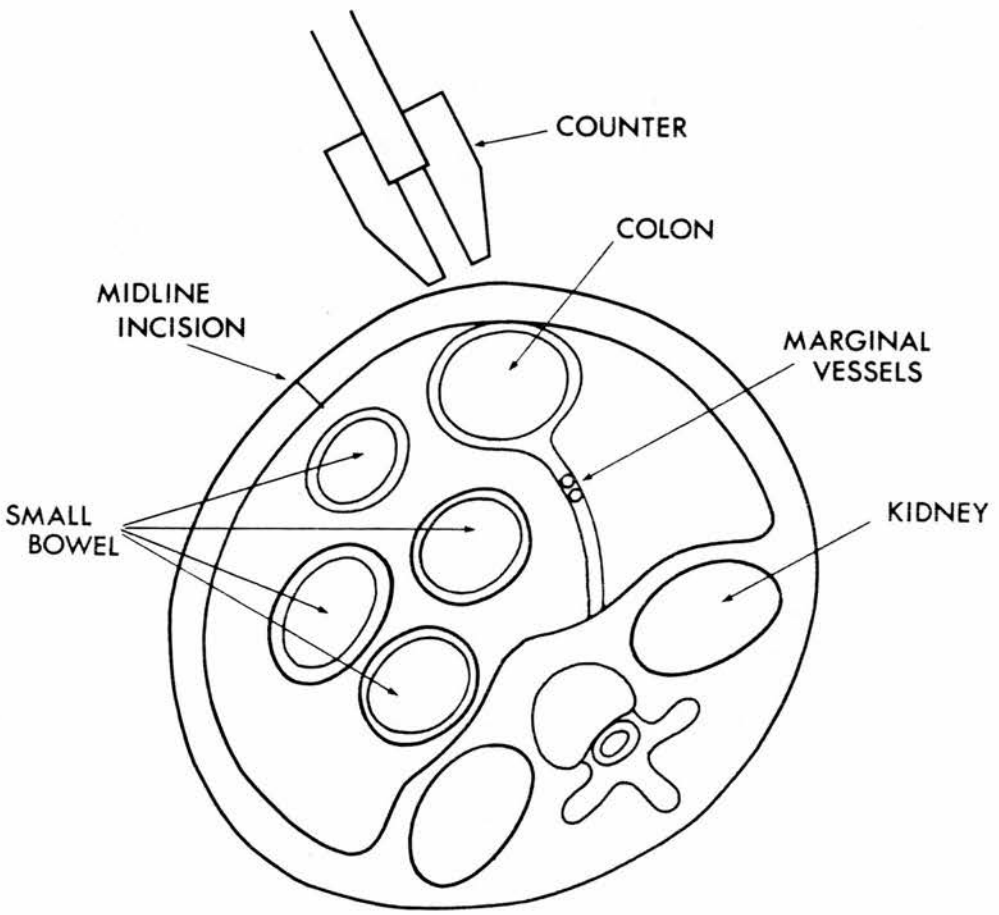
A general view of the experimental model is shown in Figure 4.7.

During stabilisation of the model and in most of the subsequent experiments, the following measurements were performed at 15 min intervals: systemic arterial pressure, pulmonary arterial pressure, heart rate, central venous (right atrial) pressure, cardiac output, core temperature and colon blood flow. In addition, 1 ml samples of arterial, mixed venous and colonic venous blood were withdrawn from the aorta, right atrium, and colonic marginal vein respectively, and analysed for pH, P_{CO_2} and P_{O_2} using an IL (Instrumentation Laboratories) 213 blood gas analyser. The acceptability of using a right atrial catheter for sampling "mixed" venous blood is discussed

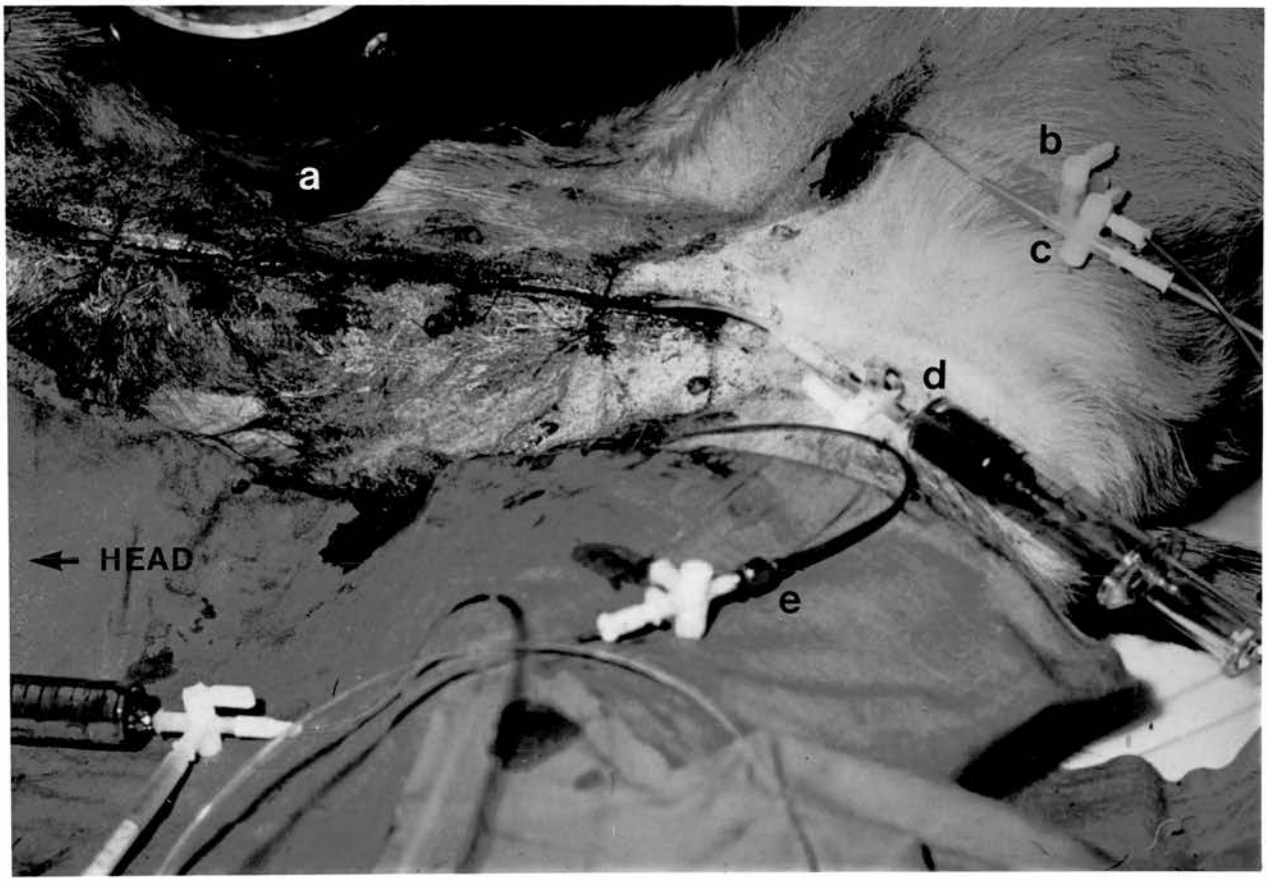


Photograph of a dog abdomen during laparotomy, showing the colon after it had been sutured to the abdominal wall. The polythene tubing passing behind the colon is connected to the marginal vein catheter.

Photograph of a dog from the tail showing the scintillation counter positioned over the two silk sutures securing the colon. The polythene tubing connected to the marginal vein catheter can be seen protruding from the lower end of the abdominal wound. The catheters and taps at the lower right of the picture are inserted into the femoral vessels.



Cross-sectional diagram through the abdomen showing the positions of colon and small bowel relative to the scintillation counter after preparation of the model.



General view of the model after preparation, showing (a) scintillation counter, (b) and (c) arterial and right atrial catheters inserted into left femoral artery and vein, (d) tubing connected to marginal vein catheter, and (e) cranial mesenteric artery catheter (for injection of xenon-133) inserted into right femoral artery.

in section [4.4.1]. The haemoglobin concentration (Hb) of the arterial sample was measured using an IL 182 co-oximeter. After withdrawing blood samples, the catheters were flushed with heparinised saline (5,000 units per 500 ml).

All blood gas measurements were corrected for any temperature difference between the animal and the analyser electrode system using a computer program based on the data of Kelman and Nunn (1966) and Roughton and Severinghaus (1973). The oxygen saturation of each sample was calculated from P_{O_2}, taking into account pH, P_{CO_2} and temperature using a computer program based on the data of Kelman (1966). Blood oxygen content was calculated using the equation:

[1] Blood oxygen content (ml dl^{-1}) =

$$\frac{\text{Hb (g dl}^{-1}) \times 1.34 \times \text{\% saturation}}{100} + P_{O_2}\ (\text{kPa}) \times 0.0233$$

Other derived values were calculated using the following equations:

[2] Colonic oxygen consumption (**ml min^{-1} 100 g^{-1}**) = $\dfrac{\text{CBF} \times \text{colonic } C_{(a-v)O_2}}{100}$

[3] Total oxygen consumption (**ml min^{-1} 100 g^{-1}**) = $Q_t \times \text{systemic } C_{(a-v)O_2} \times 10$

[4] Colonic oxygen availability (**ml min^{-1} 100 g^{-1}**) = $\dfrac{\text{CBF} \times C_{aO_2}}{100}$

[5] Colonic oxygen extraction (%) $= \dfrac{\text{colonic } C_{(a-v)O_2}}{C_{aO_2}} \times 100$

[6] Colonic vascular resistance (arbitrary units) $= \dfrac{MAP - RAP}{CBF}$

[7] Total peripheral resistance (arbitrary units) $= \dfrac{MAP - RAP}{Q_t}$

where:

CBF = colonic blood flow (ml min^{-1} 100 g^{-1}),

$C_{(a-v)O_2}$ = arteriovenous oxygen content difference (ml dl^{-1}),

C_{aO_2} = arterial oxygen content (ml dl^{-1}),

MAP = mean arterial pressure (mm Hg)

RAP = right atrial pressure (mm Hg), and

Q_t = cardiac output (litre min^{-1})

[**4.2.2**] Analysis of xenon-133 washout curves

Twenty-three washout curves from 10 dogs, representing a variety of flow rates (flow increased by adding CO_2 to inspired gas mixtures and decreased by hyperventilation - see Chapter Four) were recorded for a period of 18 min after xenon-133 (^{133}Xe) injection and analysed in detail. Exponential stripping using the tail subtraction method for analysis of multi-exponential curves (Lundgren, 1967; Selkurt and Wathen, 1967) showed that the curves recorded from the scintillation counter in these experiments consisted of three single exponential components, with a short, medium and long half-life

respectively. The assumption was made that these three components represented different flow rates in the three main tissue types in the colon, namely, mucosa, smooth muscle and submucosal connective tissue. (Evidence to justify this assumption will be presented later in this chapter).

Blood flow in each tissue was calculated from the formula of Kety (1960):

[8] $$F = \frac{k \times \lambda \times 100}{d}$$

where:

F = blood flow (ml min^{-1} 100 g^{-1}),

k = clearance constant derived from the half time ($t_{1/2}$) of the washout curve

i.e. $k = \frac{\log_e 2}{t_{1/2}}$

λ = tissue/blood partition coefficient of ^{133}Xe for the appropriate tissue, and

d = density of that tissue (g cm^{-3})

The values of λ and d were measured directly (<u>vide infra</u>).

The relative weight of each of the three types of tissue in the colon wall was determined by excising a segment of colon from each of six dogs and dividing it into its three components by stripping first the smooth muscle and then the mucosa from the tough submucosal connective tissue layer. The components were weighed separately and the average percentage distribution of the tissues calculated. Pieces of each component tissue and of the whole bowel wall were examined hist-

ologically to determine the accuracy of the separation. A value for mean colonic blood flow was then calculated for each of the 23 washout curves analysed over 18 min using the equation:

$$[9] \qquad F^{o} = \frac{(F^{a} \times W^{a}) + (F^{b} \times W^{b}) + (F^{c} \times W^{c})}{100}$$

where F^{o} = mean colonic blood flow (ml min $^{-1}$ 100 g^{-1} of colonic tissue), F^{a}, F^{b} and F^{c} = mucosal, muscle and submucosal blood flow in the same units and W^{a}, W^{b} and W^{c} = percentage weight of mucosa, muscle and submucosa in the colonic wall.

This method of analysis was found to be extremely tedious and time consuming. In addition, the manual method of exponential stripping was potentially inaccurate, particularly in respect of the calculation of the half-life of the fastest component of the exponential curve. Mathematical treatment of the first 90 sec of the original washout curve as a single exponential, and the application of the half-life of this curve to Kety's formula, was found to yield values for colonic blood flow which correlated very well with those calculated by the above lengthier method (see section [4.3.3]). It was therefore felt justifiable to use this shorter 90 sec analysis as the routine method of blood flow calculation in all subsequent experiments.

[4.2.3] Radioactive microsphere experiments

The assumption that the three uni-exponential components of the washout curves represented the three main tissue types in the colon is fundamental to the above analysis and although similar assumptions had been made for the small bowel (Selkurt and Wathen, 1967) there was little direct evidence to prove their validity. It was decided,

therefore, to use an alternative method of measuring blood flow distribution and to compare the results with those obtained by the ^{133}Xe method described above. In five dogs, an 18 min ^{133}Xe washout curve was obtained under resting conditions in the standard fashion. Subsequently, a bolus of strontium-85 (^{85}Sr) labelled microspheres of average size 15 μm and total dose 50 μCi was injected through the mesenteric artery catheter. Prior to injection, the syringe containing the microspheres suspended in sodium chloride 0.9% (0.5 - 1 ml) was agitated in an ultrasonic water bath to ensure their even distribution. As with injections of ^{133}Xe, a bolus of 4 ml sodium chloride 0.9% was injected after the injection of radioactive material. Within 5 min of injection, the dogs were sacrificed by means of a rapid intravenous injection of potassium chloride. The segment of colon which had been under the scintillation counter was then excised, and the smooth muscle and mucosa stripped from the submucosal connective tissue as previously described. Each component tissue was weighed and its gamma activity measured using an automatic gamma counter. The radioactivity in each tissue type was expressed as a percentage of total radioactivity in the bowel wall. Making the assumption that capillary diameter is essentially the same throughout the colon, these values were assumed to represent the percentage distribution of the total blood flow to each tissue type. The percentage distribution of flow was also calculated from the 18 min ^{133}Xe washout curves corresponding to each microsphere experiment by extrapolating each of the three uni-exponential components to time zero as described by Lundgren (1967) (see section [4.4.2]). The results for the two methods were found to correspond closely, providing evidence for the assumption that the three components of the

washout curve represented mucosal, muscle and submucosal flow (see section [4.3.4]).

An estimate of the degree of arteriovenous shunting in the colon and small bowel was obtained by injecting, in two animals, a second dose of microspheres (25 μCi) directly into the colonic marginal vein and comparing the radioactivity in the liver before and after this second injection. Three small pieces of liver were removed, weighed and counted for gamma activity after the initial injection into the mesenteric artery and again after the second injection into the colonic marginal vein. The percentage arteriovenous shunt was calculated from the equation:

[10]
$$S^{av} = \frac{L^1}{(L^2 - L^1) \times \frac{50}{25}} \times 100$$

where S^{av} is the percentage arteriovenous shunt, L^1 is the liver radioactivity after the first injection (into the mesenteric artery) and L^2 the liver activity after the second injection (into the colonic marginal vein). $(L^2 - L^1) \times 50/25$ (the ratio of radioactive doses) is the expected liver activity after the first injection if all the arterial blood bypassed the capillaries (100% arteriovenous shunt).

[**4.2.4**] Measurement of xenon-133 tissue/blood partition coefficients

The solubility of ^{133}Xe was measured in homogenised colon, colonic mucosa, colonic smooth muscle, and in saline and blood. The colonic submucosa could not be homogenised satisfactorily on its own and was therefore not studied separately. Samples of whole colon, mucosa and muscle from five dogs were immersed in liquid nitrogen, crushed using a precooled mortar and pestle, and one part by weight of tissue

was homogenised with two volumes of saline in a Potter homogeniser. Heparinised whole blood from three dogs was centrifuged and the plasma and cells remixed in varying proportions to give 21 samples with haemoglobin concentrations (Hb) ranging from 0 to 19 g dl^{-1}. Equilibration with ^{133}Xe at 37°C and measurement of gas/tissue partition coefficients were carried out in the manner described by Veall and Mallett (1965). The Ostwald solubility coefficients for whole colon, mucosa and muscle were calculated from the solubilities measured for homogenate and saline.

A regression analysis on the blood solubility data revealed the relationship between solubility of ^{133}Xe and Hb concentration. Since solubility varied significantly within the haemoglobin range encountered during these experiments, the equation of the regression line was used to calculate a tissue/blood partition coefficient ($\mu_{t/b}$) substituted as λ in Equation **[8]** for every blood flow measurement.

[**4.2.5**] Measurement of tissue densities

Segments of colon were excised from four dogs and separated into the three main tissue components as described previously. Glucose solutions of specific gravity from 1.04 to 1.08 (at intervals of 0.005) were prepared by appropriate dilution of a 50% solution, and poured into a series of test tubes. Small pieces of whole colon, mucosa, muscle and submucosal connective tissue were then immersed in each solution, taking care to avoid the introduction of any air bubbles. The density of each piece of tissue was recorded as that of the solution in which it remained stationary immediately after immersion. Several pieces of each tissue from each of the four dogs

were dealt with in this way.

[4.3] RESULTS

[4.3.1] General

Seventy one greyhounds were studied. No useful results were obtained from nine of the animals. In five of these the cause of failure was excessive intra-abdominal bleeding which prevented cardiovascular stability from being achieved. In four of these the source of bleeding was found to be the splenic bed and mesentery. In the fifth, an accidental injury to the aorta appeared to be the cause. A further two animals were unsuitable for study because of haematoma formation in the colonic mesentery after damage inflicted while attempting to place the venous catheter. This was always a delicate procedure and it was surprising that only two experiments were lost for this reason. In one animal the anatomy of the cranial mesenteric artery was abnormal in that there were three small colic branches rather than the usual single large common colic branch. This made it impossible to site the catheter for isotope injection in a position which would give satisfactory washout curves. The ninth failure resulted from a fault in the electronics of the counting equipment which could not be traced in time to continue the experiment.

Thus 62 experiments were available for detailed analysis. Table 4.1 shows the baseline haemodynamic data for the 62 animals. These measurements were made before undertaking any physiological or pharmacological manoeuvres. Pulmonary artery pressures were not obtained in one experiment because of failure of one of the pressure transducers. The pronounced sinus arrhythmia which occurs in the con-

TABLE 4.1 Baseline haemodynamic data from 62 dogs.

	mean	sd	sem	n
Heart rate (beat min^{-1})	158	23	3	62
Systemic arterial pressure (mm Hg)				
Systolic	168	23	3	62
Diastolic	126	17	2	62
Mean	142	18	2	62
Pulmonary arterial pressure (mm Hg)				
Systolic	16.7	6.1	0.8	61
Diastolic	9.3	4.1	0.5	61
Mean	12.8	4.9	0.6	61
Right atrial pressure (mm Hg)	0.5	1.3	0.2	62
Cardiac output (litre min^{-1})	4.1	1.2	0.2	62
Haemoglobin (g dl^{-1})	18.7	2.2	0.3	62
Core temperature (^{o}C)	37.2	0.9	0.1	62

TABLE 4.2 Baseline respiratory data from 62 dogs.

	mean	sd	sem	n
Arterial PO_2 (kPa)	14.5	1.7	0.2	62
Arterial PCO_2 (kPa)	5.3	0.4	0.1	62
Arterial pH	7.402	0.043	0.006	62
Venous PO_2 (kPa)	8.6	1.0	0.1	59
Venous PCO_2 (kPa)	6.2	0.3	0.04	59
Venous pH	7.373	0.034	0.004	59
Colonic venous PO_2 (kPa)	7.9	0.8	0.1	58
Colonic venous PCO_2 (kPa)	6.2	0.4	0.06	58
Colonic venous pH	7.371	0.022	0.003	58

TABLE 4.3 Derived data from 62 dogs.

	mean	sd	sem	n
Arterial oxygen content (ml dl^{-1})	25.33	2.52	0.32	62
Venous oxygen content (ml dl^{-1})	20.75	2.12	0.28	59
Colonic venous oxygen content (ml dl^{-1})	22.42	2.64	0.33	58
Total peripheral resistance (unit)	34.53	2.1	0.27	62
Total oxygen consumption (ml min^{-1})	188.7	70.3	9.1	59

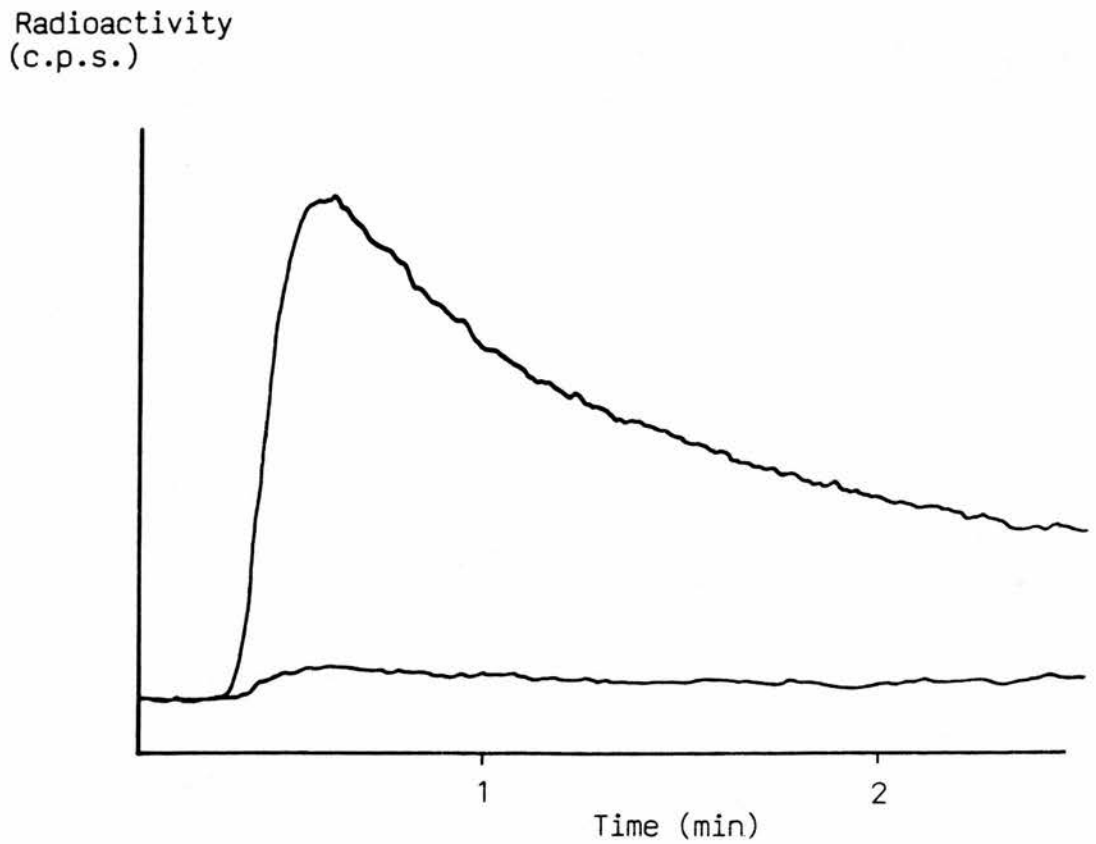
TABLE 4.3

scious dog disappeared almost completely upon institution of mechanical ventilation. Table 4.2 shows the baseline respiratory data recorded at the same stage in the experiments. In three animals which were used entirely for microsphere experiments, no venous blood gases were measured and so total oxygen consumption values were obtained for 59 animals only. Four animals were used exclusively for microsphere experiments, and had no cannula in the marginal vein. Thus, colonic venous blood was sampled in only 58 animals. The derived data from the baseline measurements are shown in Table 4.3.

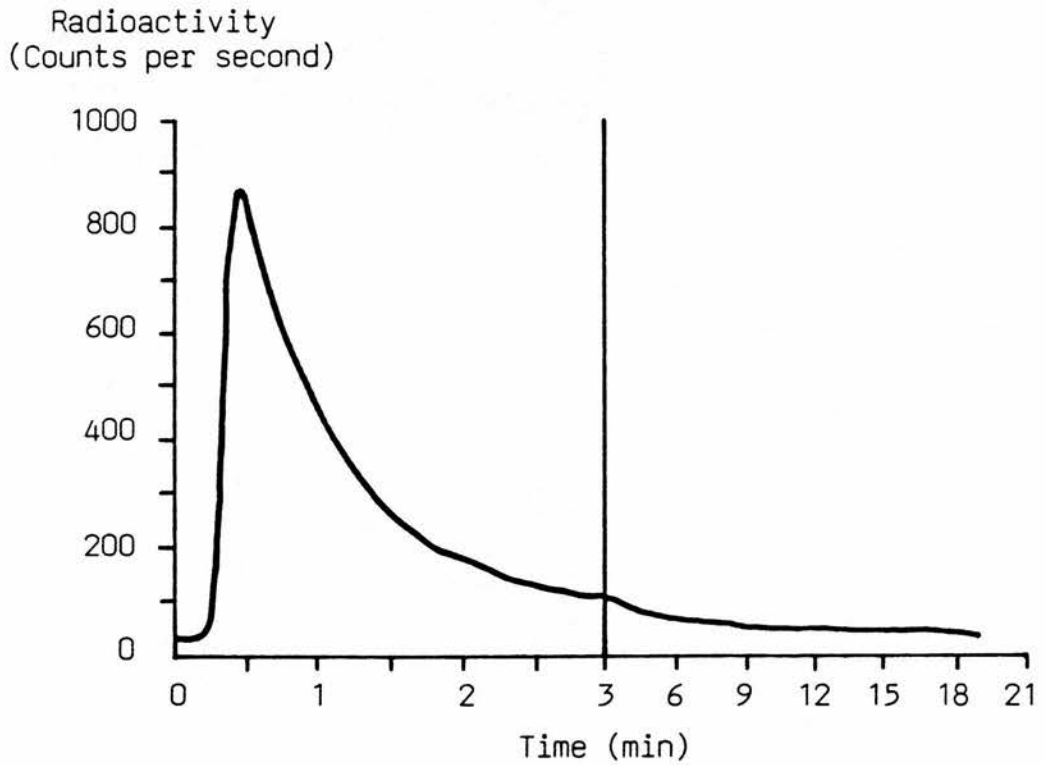
[**4.3.2**] Blood flow measurements

When radio-opaque dye was injected through the catheter in the cranial mesenteric artery, a significant proportion flowed through the common colic artery while the remainder was carried along the mesenteric artery to the small bowel (Figure 4.1). It was possible that, despite the careful positioning of the scintillation counter, a proportion of radioactivity detected by the counter came from isotope reaching the small bowel. Thus, following the injection of isotope in five animals, the mesenteric artery catheter was advanced 1.5 cm so that its tip lay just beyond the common colic branch, and the isotope injection was repeated. The effect of this manoeuvre is shown in Figure 4.8. Bearing in mind that in the experiment represented by the lower trace the entire dose of radioactivity reached the small bowel, it is clear that the quantity of radiation detected from the small bowel was negligible in comparison to the emission from the colon when the catheter was positioned correctly.

Figure 4.9 shows a typical washout curve recorded for 18 min after isotope injection. It can be seen that after 15 min the radio-



Xenon-133 washout curves (redrawn) showing radioactivity in counts per second (c.p.s.) detected by scintillation counter during the 2.5 min periods following injection of xenon-133 through the mesenteric arterial catheter before (upper trace) and after advancement of the tip of the catheter in the cranial mesenteric artery to a position distal to the common colic branch.



Typical 18 min xenon-133 washout curve (redrawn). Note the change of scale at 3 min.

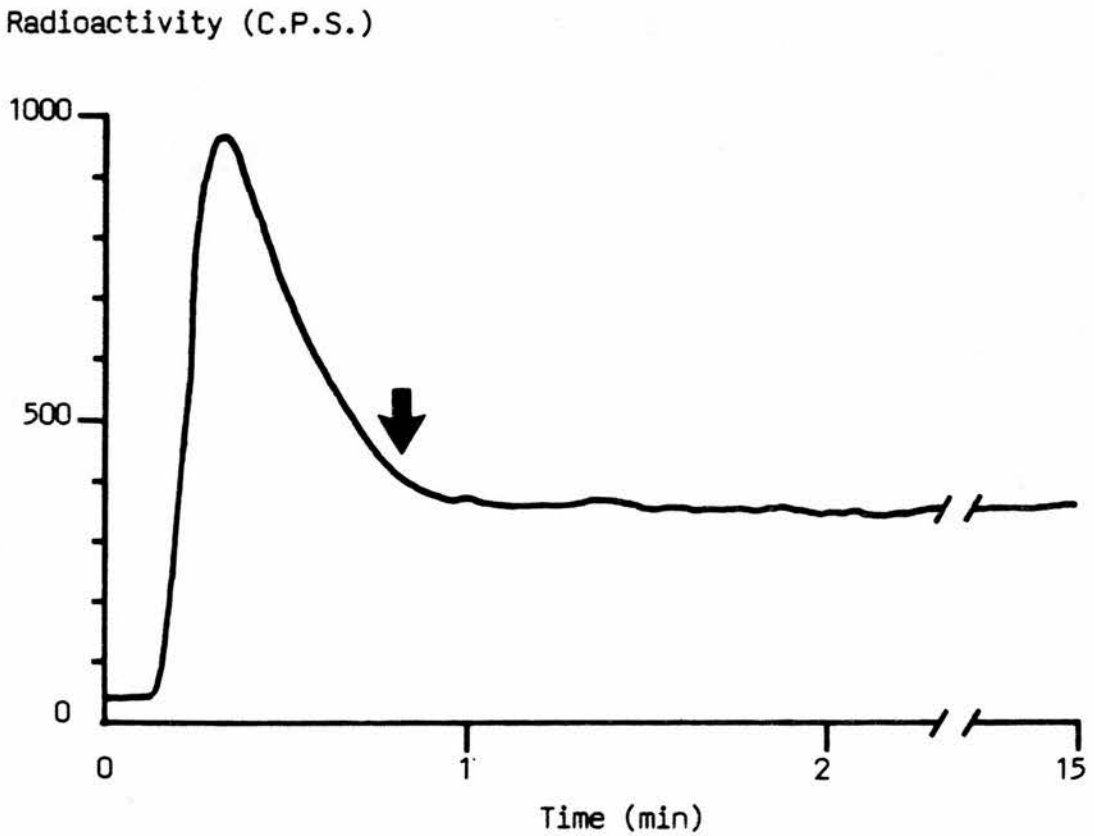
activity in the colon had returned almost to the background level. Throughout all the experiments, blood flow measurements were made every 15 min. This never resulted in excessive build-up of background radioactivity. In most recorded curves, background radioactivity was less than 10% of peak radioactivity and in no case exceeded 15%. Background radioactivity was always subtracted from the values taken from the washout curves for analysis.

The possibility that the presence of the catheter in the cranial mesenteric artery might affect the blood flow to the colon was investigated by withdrawing the catheter immediately after the isotope injection in several experiments. The curves so obtained were compared with curves produced by the standard method 15 min earlier under identical conditions apart from the presence of the catheter. Removal of the catheter made no difference to the shape of the washout curves or to the calculated flow rates.

Figure 4.10 shows the effect of sudden cardiac arrest during a washout curve. This was achieved by injecting intravenously 20 ml of a saturated solution of potassium chloride, asystole being confirmed by ECG. Twenty min after cardiac arrest, the level of radioactivity had not changed significantly from that immediately after arrest, demonstrating that the normal washout of radioactivity was due entirely to blood flow and not to diffusion into the lumen or surrounding tissues. This experiment was performed on four occasions with the same result.

[4.3.3] Analysis of washout curves

Figures 4.11 and 4.12 show the stages in the analysis of the 18 min curve shown in Figure 4.9 using the method of tail subtraction

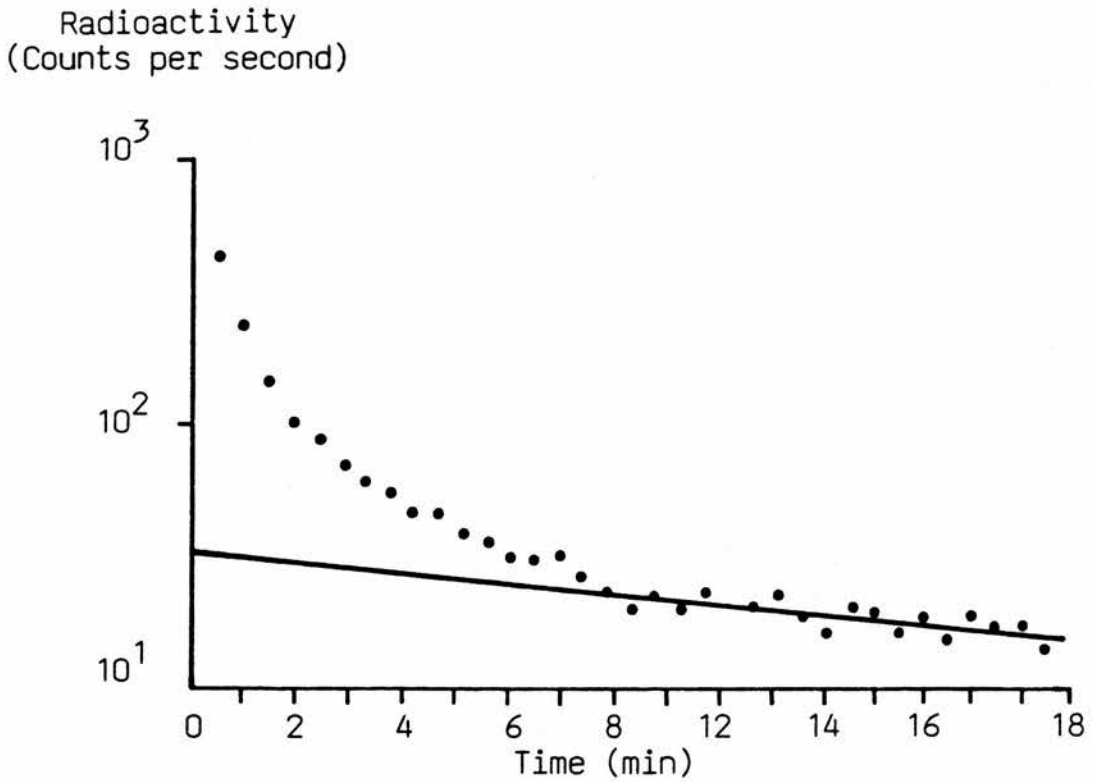


Xenon-133 washout curve (redrawn) showing the effect of cardiac arrest on decay of radioactivity from the colon. The arrow indicates the time at which cardiac arrest occurred.

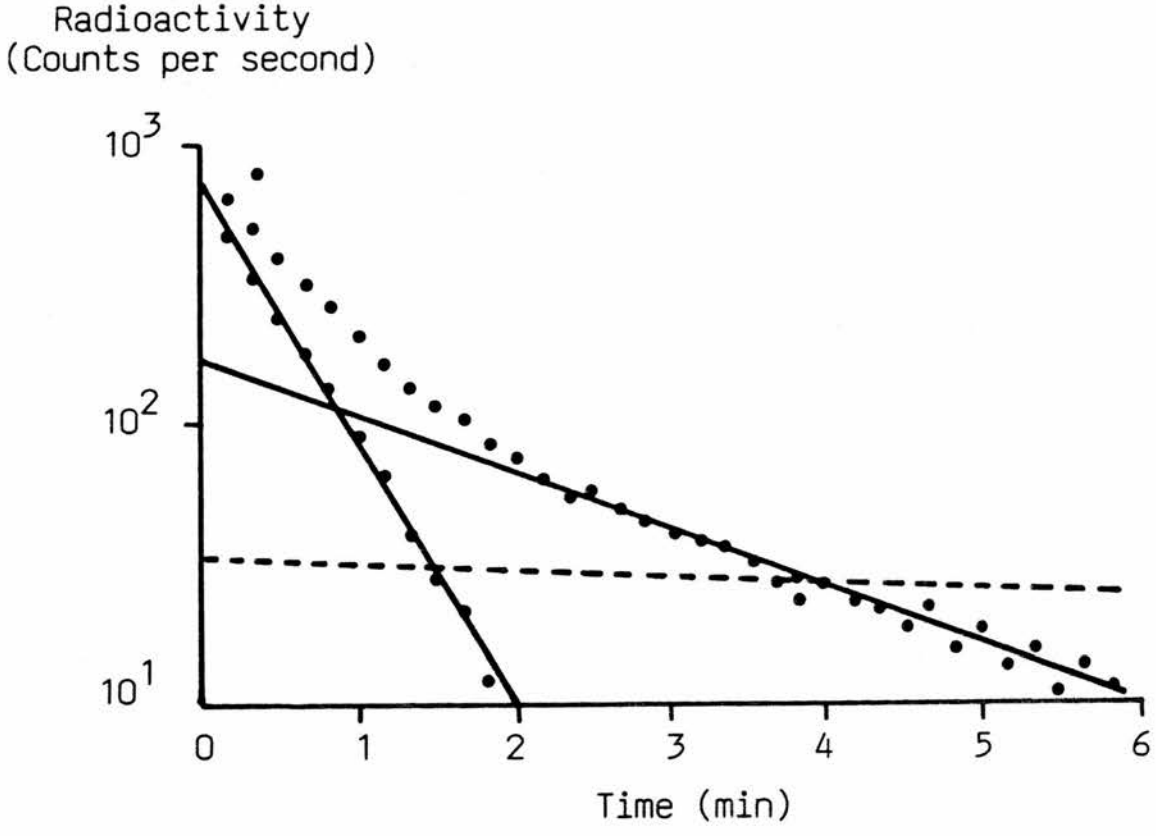
(Lundgren, 1967). Having subtracted the background radioactivity, the curve was first replotted semi-logarithmically and a straight line was drawn through the tail as shown in Figure 4.11. This line represented a slow uni-exponential component of the multi-exponential curve and was subtracted from the original curve to leave the plot shown in Figure 4.12 (note the expanded time scale). Again a line was drawn through the straight terminal portion of the curve and after subtraction on this occasion, a third straight line could be drawn through the remaining points. Thus the original multi-exponential curve was divided into three single exponential components. The calculated flow rates for the components of this particular curve were 118, 28 and 3 ml min^{-1} 100 g^{-1} for mucosa, muscle and submucosal connective tissue respectively. Substituting these values in Equation **[9]** together with the weights reported in the subsequent section for the three tissue components (Table 4.4), the mean colon blood flow was therefore:

$$\frac{(118 \times 30.6) + (28 \times 49.6) + (3 \times 19.8)}{100} = 51 \text{ ml min}^{-1} \text{ 100 g}^{-1}$$

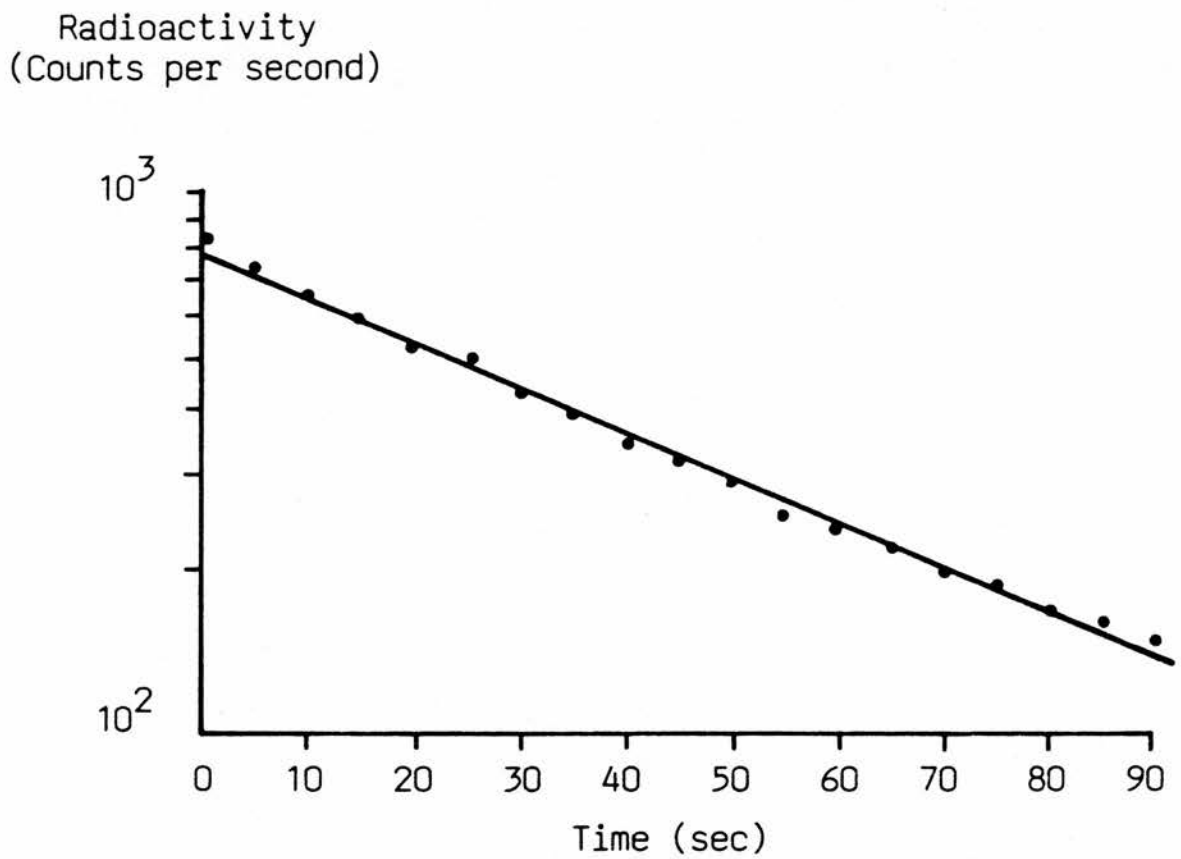
Figure 4.13 shows the alternative simpler analysis of the first 90 sec of the same curve. The background reading was subtracted and a semilogarithmic plot performed as before. Using least squares regression analysis, the line of best fit for the log(Count) vs. time data was calculated using values for radioactivity from the washout curve at 5 sec intervals, and the mean colon blood flow calculated using Equation **[8]**. The value calculated from this particular curve was 58 ml min^{-1} 100 g^{-1}. There was a good correlation between the values calculated for mean colon blood flow using the two techniques



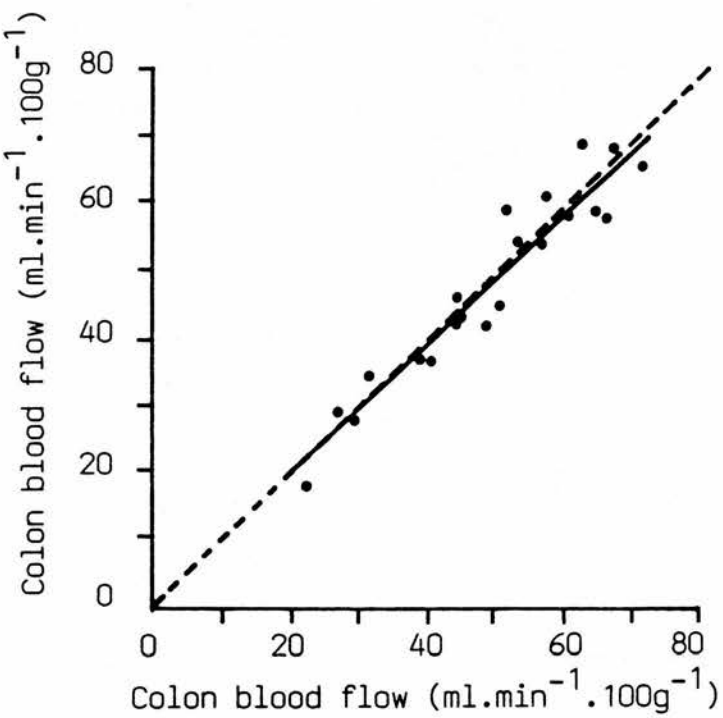
First stage of analysis of 18 min xenon-133 washout curve. The solid line is the line of best fit through the points representing the terminal exponential component of the curve.



Second and third stages of analysis of 18 min xenon-133 washout curve. Note scale difference compared with Figure 4.11. The dotted line is drawn through the terminal exponential component (off scale). The upper series of points represent the difference between values from the original washout curve and values at the corresponding times on the line drawn through the tail of the curve. The line of best fit has been drawn through the tail of the new set of points. The subtraction process has been repeated to produce the lower set of points, and the line of best fit drawn through these represents the fast component of the decay curve.



Line of best fit calculated by least squares regression analysis through data points taken from the first 90 sec of xenon-133 washout curve.



Relationship between 23 pairs of colonic blood flow measurements calculated from analysis of 90 sec (vertical axis) and 18 min (horizontal axis) washout curves. The dotted line is the line of identity.

on 23 pairs of washout curves (Figure 4.14). The equation of this regression line is $y = 0.97x + 0.71$ and the correlation coefficient is 0.96 ($p < .001$).

[**4.3.4**] Microsphere and related experiments

The histology of the separated layers of the colon compared to the intact colon showed that accurate separation of the mucosa and smooth muscle was achieved, although the muscularis mucosae invariably remained attached to the submucosal connective tissue layer. However, the amount of tissue in the muscularis mucosae was so small compared to that in the main muscle mass and in the connective tissue that it was considered justifiable to ignore it. It was also noted from the histology that there was very little fat in any of the layers of the colon.

The relative weights of the three tissue components of the colon from six dogs are shown in Table 4.4. The mean values were used in Equation **[9]** for calculating mean colon blood flow from the 18 min washout curves (see example in section [4.3.3]).

There was a close correlation between initial radioactivity in the fast, medium and slow components of the ^{133}Xe washout curves (calculated by extrapolation to time zero - see section [4.4.2]) and the radioactivity in the mucosa, muscle and submucosa after microsphere injection (Table 4.5). This provides strong presumptive evidence that the three components of the washout curves did indeed represent flow in the three main tissue compartments.

The percentage arterio-venous shunt in the colon and small bowel calculated as described in section [4.2.4] was 8.6%.

TABLE 4.4 Percentage weight of mucosa, muscle and submucosal connective tissue in colon from six dogs.

	Mucosa	Muscle	Submucosa
mean	30.6	49.6	19.8
sd	3.2	4.4	1.8
sem	1.3	1.8	0.7

TABLE 4.5 Comparison between initial radioactivity in the components of the xenon-133 washout curves and the radioactivity in the mucosa, muscle and submucosa after microsphere injection. The figures from five experiments are expressed as mean (sem) percentages of total radioactivity.

	Fast component	Medium component	Slow component
xenon-133 curves	54 (4)	38 (4)	8 (1)
	Mucosa	**Muscle**	**Submucosa**
Microspheres	57 (6)	39 (5)	4 (1)

[**4.3.5**] Tissue/blood partition coefficients

The Ostwald solubility coefficient for ^{133}Xe in dog colon was 0.751 ± 0.038 mmol litre^{-1} kPa^{-1} at 37°C (mean ± sem). The values for colonic mucosa and for colonic muscle were not significantly different from this value. This observation was not unexpected since the presence of fat is the main factor responsible for increasing xenon solubility and it was evident from the histology that there was very little fat in any of the greyhound colonic tissues. The relationship between solubility coefficient and haemoglobin concentration (Hb) is shown in Figure 4.15. The solubility coefficient for dog blood may be calculated from the equation of the regression line:

$$\text{solubility coefficient} = 0.042\ Hb + 0.705$$

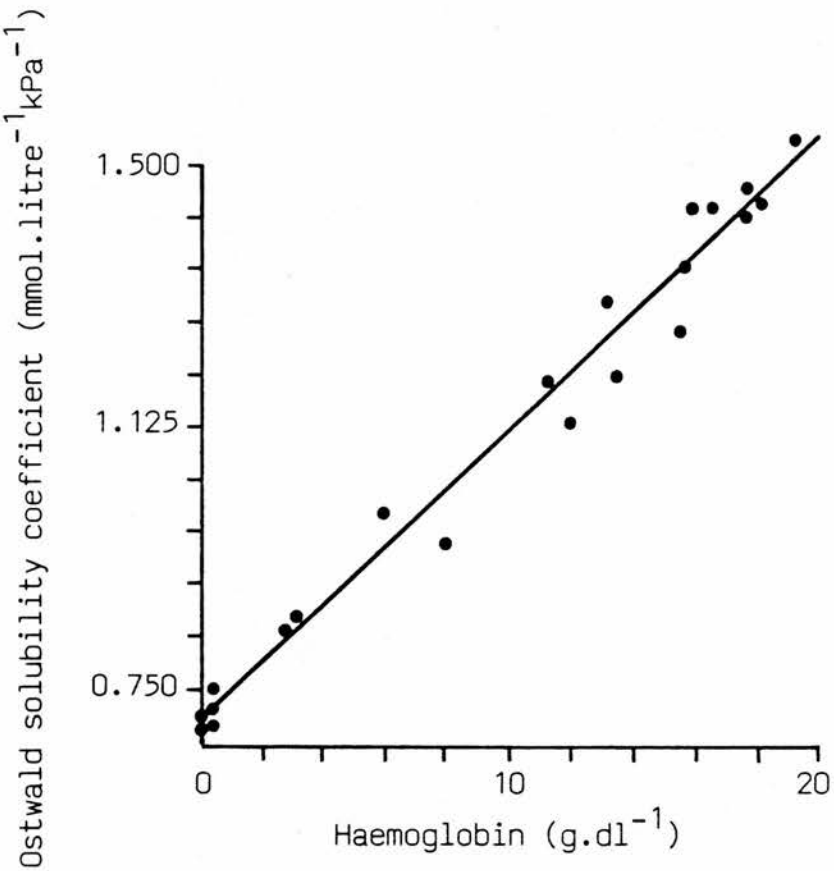
The tissue/blood partition coefficient ($\mu_{t/b}$) is the ratio of these solubilities:

$$\mu_{t/b} = \frac{0.751}{0.042\ Hb + 0.705}$$

Thus, for Hb = 12 g dl^{-1}, $\mu_{t/b}$ = 0.62, while for Hb = 20 g dl^{-1}, $\mu_{t/b}$ = 0.49.

[**4.3.6**] Tissue densities

The measured densities of the three component tissues did not differ significantly from each other or from that of the whole colon (Table 4.6), a finding which was not unexpected in view of the lack of fat in any of the tissues.



Relationship between haemoglobin concentration and Ostwald solubility coefficient (tissue/blood) for colon. Data from a total of 21 samples from five dogs. The equation of the regression line is:

$y = 0.042x + 0.705$ $r = 0.86$ $p < 0.001$

TABLE 4.6 Densities (g cm^{-3}) at 20°C of whole colon and its three main layers in specimens from four dogs.

	Whole Colon	Mucosa	Muscle	Submucosa
mean	1.065	1.063	1.067	1.067
sd	0.0005	0.003	0.001	0.009
sem	0.0003	0.0016	0.0005	0.004

TABLE 4.6

[**4.3.7**] Basal colon blood flow and oxygen consumption

Table 4.7 shows the basal colon blood flow and colonic vascular resistance in 62 animals calculated from the first 90 sec of the washout curve, and basal colon oxygen consumption in 58 animals. Colonic oxygen consumption could not be calculated in four animals which were used exclusively for microsphere experiments and had no cannula in the colonic marginal vein. The coefficient of variation for consecutive blood flow measurements was 9.1% calculated from the equation:

$$\text{coefficient of variation} = \frac{\text{standard deviation of differences between consecutive measurements}}{\text{mean of measurements}} \times 100$$

Table 4.8 shows the blood flows calculated as described above from 18 min washout curves from 10 animals. The three components of these washout curves, which were obtained under resting conditions, represent basal mucosal, smooth muscle and submucosal blood flows.

[**4.4**] DISCUSSION

[**4.4.1**] The experimental model

The model was designed to simulate as closely as possible the clinical situation of a patient undergoing routine abdominal surgery. Intermittent positive pressure ventilation was necessary to obtain accurate control of arterial P_aCO_2, this being achieved satisfactorily as can be seen from Table 4.2. The anaesthetic and relaxant agents used (pentobarbitone and pancuronium) were chosen because of their known minimal pharmacological effect on the cardiovascular system (Kelman and Kennedy, 1971; Hall, 1971).

TABLE 4.7 Basal colonic blood flow and derived parameters from 62 dogs.

	mean	sd	sem	n
Colonic blood flow (ml min^{-1} 100 g^{-1})	39.9	6.8	0.9	62
Colonic vascular resistance (unit)	3.54	1.26	0.16	62
Colonic oxygen consumption (ml min^{-1} 100 g^{-1})	1.16	0.38	0.05	58

TABLE 4.7

TABLE 4.8 Basal blood flow (ml min^{-1} 100 g^{-1}) in mucosa, muscle and submucosa calculated from the three components of the xenon-133 washout curves. Ten experiments in six dogs.

	Mucosa	Muscle	Submucosa
mean	100.1	25.0	2.8
sd	14.9	5.3	0.6
sem	4.7	1.7	0.2

The anaesthetic and surgical techniques employed are unlikely to have influenced colonic haemodynamics. Bond, Prentiss and Levitt (1980) demonstrated that following induction of anaesthesia in dogs with pentobarbitone 30 mg kg^{-1}, colonic blood flow measured using a microsphere injection technique increased significantly 15 min after induction compared with baseline levels in the conscious dog, but at 60 min after induction, returned to a value not significantly different from control. In addition, they found that laparotomy, consisting of a midline incision through the abdominal wall, had no significant effect on colonic blood flow.

In the animal model described here, the favourable properties of the drugs selected were confirmed in practice in that once haemodynamic stability had been achieved, small incremental doses of either or both drugs did not significantly affect colon blood flow or systemic haemodynamics. Insertion of monitoring catheters and laparotomy occupied a period of 45 - 90 min after induction of anaesthesia, and a stabilisation period of 60 min was invariably allowed before the experimental protocols described in this and subsequent chapters were begun.

Splenectomy was performed in all dogs to eliminate the complicating effects of the contractile canine spleen. Chien and others (1973) demonstrated that splenectomy in the dog results in a model which simulates more closely the human cardiovascular response to stress.

Most previous attempts at measuring colon blood flow have either been qualitative (Grayson, 1951; Welsh, 1963) or if quantitative, have involved isolated or exteriorised loops of gut (Hultén et al., 1976a; Hanson and Moore, 1969) or have used micro-

spheres, a technique which requires that the animal be killed after one, or, if different isotopes are used, two measurements (Bond, Prentiss and Levitt, 1980). Quantitative methods measuring small bowel flow have also been relatively invasive (Selkurt and Wathen, 1967; Lundgren, 1967; Wilson et al., 1975). The model described here induced virtually no trauma to the gut or mesentery, which were left intact in their natural intra-abdominal positions. The mesenteric arterial and venous catheters caused no significant obstruction to flow. The abdomen was closed so that temperature changes and dehydration due to exposure of the gut to the atmosphere were not significant factors. Thus repeated measurements of blood flow and oxygen consumption were made in conditions which were as "physiological" as is possible with any experimental model measuring these parameters.

The use of right atrial blood for measurement of venous P_{O_2} introduces a small error into the calculation of total oxygen consumption. Right atrial sampling was undertaken because of difficulties in sampling from the very narrow lumen of the pulmonary arterial catheter. In a small number of animals, some pulmonary arterial blood samples were obtained and yielded values for arteriovenous oxygen content difference which were less than 10% lower than those calculated using values from right atrial blood sampled simultaneously. As total oxygen consumption was calculated only for comparison with changes in colonic venous oxygen consumption, and in view of the wide scatter of total oxygen consumption values, it was felt that right atrial blood sampling for this purpose was acceptable.

[**4.4.2**] Analysis of xenon-133 washout curves

The theoretical background to the use of radioactive isotopes in the measurement of tissue blood flow was originally developed and described by Kety (1951, 1960) and has been reviewed extensively by Lundgren (1967) and Sejrsen (1971). The basic premise on which the method depends is that the rate of disappearance of a lipid soluble gas from a tissue is directly proportional to the rate of perfusion of the tissue.

Certain assumptions are fundamental to the accuracy of such a method. These are:

1) that the gas is metabolically inert,
2) that the gas is freely diffusible across the entire capillary wall and that tissue/blood diffusion equilibrium is reached virtually instantaneously,
3) that the gas leaves the tissue only via the blood, and
4) that the gas is entirely removed from the circulation during the first passage through the lungs.

These criteria have been shown to be met acceptably well by the lipid soluble radioactive inert gases krypton-85 (^{85}Kr) and ^{133}Xe.

The blood flow in a tissue or tissue compartment may be calculated from the washout curve after intra-arterial injection of the isotope from Kety's formula (Equation **[8]** above). This formula assumes that the flow rate is constant during the recording of the washout curve.

Where the tissue under study is homogeneously perfused, a single exponential washout curve describes the decay of radioactivity recorded. This is true of the myocardium (Johansson, Linder and Seeman, 1964) and of the testis (Setchell, Waites and Thorburn,

1966). The situation is more complex, however, when the tissue consists of two or more compartments with different flow rates. In this event, a multi-exponential washout curve is obtained. For a tissue with three compartments, and again assuming that blood flow is constant during the recording period, washout of gamma activity after intra-arterial injection of ^{133}Xe can be described by the equation:

[11] $$A_t = (A_1 \times e^{-k_1 t}) + (A_2 \times e^{-k_2 t}) + (A_3 \times e^{-k_3 t})$$

where A_t = total activity at time t, A_1, A_2 and A_3 = initial activity present in each compartment, and k_1, k_2 and k_3 = clearance constants of each compartment. The A and k values of the three compartments are calculated by exponential stripping, as described above. The A values are obtained from the extrapolation of each component to time zero (i.e. the intercept of each component exponential curve on the y-axis) and the k values from the slope of each component.

Zierler (1965), and Bassingthwaighte, Strandell and Donald (1968) adopted a different approach to the analysis of washout curves, based on measurement of the area under the curve. This method was not used in the present experiments since it seemed much less precise in a situation where flow appeared to be quite accurately compartmentalised.

Several possible criticisms of the technique used in the present blood flow measurements arise from these theoretical considerations and require comment.

It is possible that recirculation of ^{133}Xe could have contributed to one or more of the components of the washout curve. However, it is likely that, at most, 5% of the isotope passing

through the lungs would have re-appeared in the arterial circulation (Chidsey et al., 1959). Only a small proportion of the mass of recirculated ^{133}Xe would have been distributed to the colon, and thus its contribution to the radioactivity detected by the scintillation counter over the colon would have been very small.

A proportion of the isotope might have left the colonic tissue by routes other than the blood stream, e.g. in lymph, or by diffusion into the lumen or the tissues surrounding the colon. However, the volume flow of intestinal lymph is known to be less than 0.2% of that of blood (Wilson, 1962) and so the quantity of any isotope leaving by that route would have been insignificant. Two pieces of experimental evidence exclude the possibility of significant diffusion into the lumen or surrounding tissues. Firstly, even after as many as 25 blood flow measurements at 15 min intervals, there was minimal build-up of background radioactivity, and secondly, instantaneous cardiac arrest resulted in the immediate cessation of the washout curve with no further decay in activity over a 20 min period (Figure 4.10).

Any suggestion that the colon blood flow may have varied during recording of a curve, thus invalidating the analysis, can only be answered by stating that all flow measurements were made at least 10 min after any change in circumstances which might affect flow, thus allowing a reasonable time for stabilisation. While it is true that some adaptation to the increased flow resulting from hypercapnia was noted (see Chapter Five), this occurred over a period of about 40 min and was unlikely to have been significant over the first 90 sec. This potential criticism was, however, an additional factor in the decision to adopt the initial 90 sec analysis as the routine method of determining blood flow.

The fact that the washout curves obtained in these experiments could be resolved into three uni-exponential components as described does not automatically imply that the components had any physiological significance in the sense that they represented the washout from particular compartments of the colon. No other detailed analysis of the washout of gamma activity from the colon has been reported but several such analyses have been performed on small bowel. Kampp, Lundgren and Sjösstrand (1968), using ^{85}Kr in the cat small bowel, found multi-exponential washout curves which resolved into four components, including a very rapid initial component which was thought to reflect a countercurrent exchange of krypton between the ascending and descending limbs of the vascular loops in the mucosa. The other three components were thought to represent flow in mucosa, muscle and perivascular mesenteric fat respectively. Corroborative evidence for the localisation of the components was provided by several complementary methods, including the recording of ^{85}Kr ß activity from both the mucosal and serosal surfaces of the bowel. Norris and Sumner (1974) also found four components in ^{133}Xe washout curves obtained from the small bowel of mongrel dogs but they based their analysis entirely on the work of Kampp and his colleagues. Selkurt and Wathen (1967) found only three components in ^{133}Xe washout curves from canine small bowel. The ratios of components were very similar to those found in the present analysis of curves from the greyhound colon. The average flow values for each component were 148.8, 35.7 and 3.4 ml min^{-1} 100 g^{-1}, these values being almost identical in proportion to those quoted from the present experiments in Table 4.8. Selkurt and Wathen suggested that their three components were derived from the mucosal glandular epithelium, the smooth muscle and the con-

nective tissue respectively. However, their evidence for this was indirect, and consisted of the fact that having made this assumption, the calculated mean, or "total", blood flow correlated with the total flow measured by a direct electromagnetic flow probe technique.

In the present studies, the close correlation between the extrapolated initial ^{133}Xe concentration from the three components of the washout curves from the colon, and the radioactivity in the mucosa, muscle and submucosal connective tissue after microsphere injection (Table 4.5), provides strong direct evidence to support the assumption that the three components represent mucosal, smooth muscle and submucosal connective tissue flow. The main difference between this analysis and that of Kampp, Lundgren and Sjösstrand (1968) is the absence of the initial rapid component and this may be due to an anatomical and/or physiological difference between the blood supply of the mucosa in the dog colon and the cat small bowel. Presumably either there was little or no countercurrent exchange taking place in the mucosa of the colon in the present experiments, or any such exchange was so rapid that it was not detectable by the technique used.

Since all layers of the bowel wall take part in the healing process, the mean colon blood flow was the value of most relevance for the purpose of the subsequent experiments. Furthermore, it has been demonstrated that blood flows to mucosal/submucosal and muscle layers of the bowel increase in parallel in response to pentobarbitone anaesthesia (Bond, Prentiss and Levitt, 1980), injection of glucagon (Bond and Levitt, 1980) and sympathetic stimulation (Hultén, Lindhagen and Lundgren, 1977), and decrease together in response to haemorrhage (Bond and Levitt, 1980), and severe intra-

luminal distension (Ruf et al., 1980).

[**4.4.3**] Microsphere experiments

The application of the microsphere method to the measurement of organ or tissue blood flow is based on the principle that spheres dispersed in arterial blood pass to and lodge in each tissue in exact proportion to the tissue's blood flow. The method has been validated by others (Neutze, Wyler and Rudolph, 1968) by simultaneous measurement of blood flow with microspheres and electromagnetic flow meters. The use of microspheres to measure distribution of flow to various tissue layers has been validated by Micflikier and others (1976), who compared intestinal villus blood flow simultaneously using radioactive microspheres and a carbon monoxide uptake method.

The main purpose of the ^{85}Sr microsphere experiments was to provide evidence for the anatomical identification of the components of the washout curves, as has already been discussed. Bond, Prentiss, and Levitt (1980), using injections of either ytterbium-169 or ^{85}Sr labelled microspheres, found a mean resting colonic blood flow of 44 ml min^{-1} $100g^{-1}$, 45.9% of which was distributed to the mucosa. A similar calculation on data from the present studies using microspheres (Tables 4.4 and 4.5) yields a mean total colonic blood flow of 44.5 ml min^{-1} 100 g^{-1}, with 39.1% distribution to the mucosa.

Bond and Levitt (1979) demonstrated by the use of two separate injections 8 min apart of differently labelled microspheres that the gut blood flows calculated were not significantly different from each other, suggesting that injection of microspheres per se does not alter blood flow. In addition, they found by taking repeated tissue samples over a 1 hr period that microspheres which became impacted in

the capillaries upon injection did not migrate subsequently. In the present experiments, larger microspheres were used, and the animals killed within 5 min of injection,

The additional information on the amount of arteriovenous shunting present in the canine mesenteric circulation is also of some interest. Bond, Prentiss, and Levitt (1980) estimated arteriovenous shunt fraction across the gut to be approximately 30%, but the microspheres which they used were only 7 to 10 μm in size, compared with the 15 μm microspheres used in the present studies. Grim and Lindseth (1958), using a similar technique, estimated arteriovenous shunt fraction of the dog intestine to be only about 4% of total intestinal flow. The figure of 8.6% from the present work is based on only two experiments but nevertheless does confirm that any such arteriovenous shunting is likely to be small. Any ^{133}Xe passing through such shunts would presumably do so within the first few seconds after injection and would therefore not contribute significantly to the washout curve.

[**4.4.4**] Basal colon blood flow and oxygen consumption

The value obtained for mean basal colon blood flow (39.9 ml min^{-1} 100 g^{-1} - Table 4.7) is similar to that found by Hanson and Moore (1969) in the dog although their method utilised an electromagnetic flowmeter and an isolated perfused colon preparation. Bond, Prentiss, and Levitt (1980) found mean basal colon blood flow in the dog to range between 34 and 44 ml min^{-1} 100 g^{-1} in a series of experiments. Hultén and others (1976a) reported a value of 22 ml min^{-1} 100 g^{-1} for cat colon. Bacaner (1966) found that human colon blood flow was about 70 - 80 ml min^{-1} 100 g^{-1}, but this surprisingly

high figure may have been due to the fact that his intraluminal Geiger-Müller tube was recording radioactivity mainly from the mucosa. Values for small bowel have varied from 64 ml min^{-1} 100 g^{-1} in the dog (Selkurt and Wathen, 1967) through 30 - 35 ml min^{-1} 100 g^{-1} in the cat (Kampp and Lundgren, 1968) to 28 ml min^{-1} 100 g^{-1} again in the cat (Hultén et al., 1976a). The result for basal blood flow in Table 4.7 would seem, therefore, to suggest that more invasive techniques have given results at least in the correct order of magnitude.

There have been no previous reported estimates of colon oxygen consumption. However, Shepherd (1978) measured oxygen consumption in isolated loops of small bowel, and his mean value of 1.90 ml min^{-1} 100 g^{-1} appears to be in reasonable proportion to that of 1.16 ml min^{-1} 100 g^{-1} for colon in the present studies, taking into account the greater oxygen requirements of small bowel for secretion and absorption. The ratio of blood flow to oxygen consumption appears to be higher in the bowel than in many other organs, e.g. the brain, in which blood flow in the adult is around 54 ml min^{-1} 100 g^{-1} and oxygen consumption about 3.5 ml min^{-1} 100 g^{-1} (Ganong, 1977). This is not surprising, since in addition to supplying its metabolic oxygen requirements, the blood flow to the bowel supplies fluid for gland secretion and also acts as the major transport medium for absorbing products of digestion.

[4.5] CONCLUSION

The animal model appeared to provide values for colonic blood flow which were not dissimilar from those reported by other investigators. In addition, flow measurements were reproducible in a steady state. Values for oxygen consumption appeared to be compatible

with those available for comparison. The model was cardiovascularly stable, and repeated measurements could be made. It was therefore considered appropriate to proceed with a series of experiments to investigate the effects on colonic blood flow and oxygen consumption of a variety of factors pertinent to the peri-operative period.

CHAPTER FIVE

THE EFFECTS OF HYPOCAPNIA AND HYPERCAPNIA

[5.1] INTRODUCTION

Having established a reproducible model to measure colonic blood flow and oxygen consumption, it was felt appropriate for two reasons to investigate the effects upon these parameters of changes in arterial P_{CO_2}. Firstly, it is known that carbon dioxide has a direct local vasodilating effect on arterioles in myocardium (Ledingham et al, 1970), brain (Skinhøj and Paulson, 1969) and small bowel (Svanvik, Tyllström and Wallentin, 1968), and it appeared reasonable to suppose that a similar effect would occur in the colon, thus providing a test of the sensitivity of the model. Secondly, changes in P_aCO_2 would be of clinical interest. Hypocapnia is common when mechanical ventilation of the lungs is employed during surgery and in critically ill patients (e.g. severe sepsis, multiple trauma). Hypercapnia may occur during the post-operative period, is often associated with the injudicious use of opioid drugs, and affects particularly patients with pre-existing pulmonary disease.

[5.2] METHODS

[5.2.1] Introduction

The effect on colonic blood flow of acute changes in P_{CO_2} was investigated in a total of 46 animals. Thirty-five of these dogs had already been studied to obtain the baseline measurements detailed in Chapter Four. Following preparation of the model, a period of 60 to 90 min was allowed for stabilisation.

[5.2.2] Acute hypocapnia

In 23 animals (Group 1), acute hypocapnia to produce an arterial P_{CO_2} of between 2 and 4 kPa was induced by hyperventilation using a tidal volume between 50 and 75% greater than that resulting in normocapnia in the particular animal. Twenty experiments were conducted by increasing the tidal volume immediately after the control measurements had been made. When the end-tidal carbon dioxide concentration had reached a plateau, and no sooner than 15 min after the control measurements had been made, all measurements were repeated. In seven experiments, hyperventilation was undertaken as described, and following measurements made at hypocapnia, carbon dioxide was added to the inspired gas mixture to produce normocapnia. Following another set of measurements at normocapnia, the administration of carbon dioxide was discontinued, and measurements repeated. The two techniques were used in order to separate the possible mechanical effects on the cardiovascular system of increased tidal volume and intrathoracic pressure from the effects of hypocapnia. Tidal volume was then restored to its original setting, and all variables measured again after a further 15 min period.

In a separate series of experiments on another 23 animals (Group 2), acute hypocapnia to an arterial P_{CO_2} of between 2.1 and 3.1 kPa was induced by hyperventilation after a control series of measurements, and a complete set of measurements made 15 min later. In addition to the routine measurements, arterial, right atrial and colonic venous blood were sampled simultaneously in 11 dogs for subsequent measurement of blood lactate and pyruvate concentrations using methods described in section [5.2.6].

[5.2.3] Acute hypercapnia

Acute hypercapnia was induced by the addition of carbon dioxide to the inspired gas mixture. In the 23 animals in Group 1, the degree of hypercapnia for each experiment was selected randomly within the range of 6 to 16 kPa. A total of 59 experiments were undertaken, and in each, the flow rate of carbon dioxide added to the inspired gas mixture was adjusted to produce an end-tidal carbon dioxide concentration approximating to the target P_aCO_2. After a 15 min period, measurements of cardiovascular parameters, colonic blood flow, and arterial, right atrial and colonic venous blood gas tensions were made. The inspired gas mixture was then returned to its original composition, and all measurements were repeated 15 min later.

In Group 2, hypercapnia was induced by the same means to an arterial P_{CO_2} of between 10.0 and 12.5 kPa following a set of control measurements. All measurements were repeated 15 min later. In 11 of the animals, samples were obtained for measurement of blood lactate and pyruvate concentrations.

[5.2.4] Prolonged hypercapnia

Five dogs were subjected to prolonged hypercapnia. Following a 60 min period for stabilisation after laparotomy, four sets of control measurements were made at 15 min intervals. Hypercapnia was induced by addition of carbon dioxide to the inspired gas mixture, and maintained for a period of 75 min. Measurements were performed every 15 min. Normocapnia was restored, and the measurements repeated at 15 min intervals for a further 45 min.

[5.2.5] Prolonged hypocapnia

In the same animals, hypocapnia was induced by increasing the tidal volume no sooner than 60 min after the restoration of normocapnia. Hypocapnia was maintained for a period of 75 min, and tidal volume was then restored to its original value. Measurements were recorded every 15 min for 45 min before hypocapnia was induced, during the period of hypocapnia, and for the succeeding 60 min.

[5.2.6] Measurement of blood lactate and pyruvate concentrations

Blood lactate and pyruvate concentrations were measured using an enzymatic method in which the lactate dehydrogenase/NADH system was employed (Davidson, 1978). A reaction-rate mode of measurement was used for lactate, and an end-point technique for pyruvate. For the range of values obtained in these experiments, the within-batch coefficient of variation was 4.9% for lactate and 7.6% for pyruvate, and the between-batch coefficients of variation were 4.3% and 8.6% respectively.

[5.2.7] Statistical analysis

In the experiments described in this and the succeeding chapters, the following statistical tests were used. Student's paired and unpaired t-tests were used for the calculation of the significance of differences in measurements within and between groups of animals respectively. Least squares regression analysis was used for calculating the significance of relationships between measurements. The significance of differences between the slopes of regression lines was calculated using the method described by Petrie (1978). A probability value of less than 0.05 was taken to indicate statistical

significance.

[5.3] RESULTS

[5.3.1] Acute changes in P_aCO_2 - Group 1

Table 5.1 shows the changes in heart rate, cardiac output, mean arterial pressure, colonic blood flow and colonic vascular resistance in seven experiments during hypocapnia induced by hyperventilation, normocapnia during hyperventilation with gas containing added carbon dioxide, and hypocapnia induced by removing the carbon dioxide from the inspired gas mixture. There were statistically significant decreases in mean arterial pressure ($p < 0.02$) and colonic blood flow ($p < 0.01$), and a significant increase in colonic vascular resistance ($p < 0.05$), between values at normocapnia and hypocapnia irrespective of the presence of hyperventilation. No significant alterations in cardiac output or heart rate occurred. There were no significant differences in any parameter between measurements made at normocapnia with or without hyperventilation, or between measurements made on either occasion during hypocapnia.

In all experiments, hypocapnia resulted in a decrease in colonic blood flow, and hypercapnia in an increase. In 20 experiments undertaken during acute hypocapnia, mean colonic blood flow decreased by 22% (Table 5.2). During hypercapnia, the increase in colon blood flow became greater as P_aCO_2 increased to between 10.1 and 12 kPa (Figure 5.1). At this degree of hypercapnia, there was an increase in mean colonic blood flow of 78.2%. At higher values of P_aCO_2, the increases in colonic blood flow were of a progressively smaller magnitude. There was a highly significant relationship ($r = 0.80$, $p < .001$) between P_aCO_2 and colonic blood flow at arterial carbon dioxide

TABLE 5.1 The effects of hyperventilation with and without hypocapnia on heart rate, cardiac output, mean arterial pressure, colonic blood flow and colonic vascular resistance. Values, expressed as mean (sem), from seven dogs.

		Hyperventilation			
	Normocapnia	Hypocapnia	Normocapnia (+ CO_2)	Hypocapnia	Normocapnia
Arterial PCO_2 (kPa)	5.57 (0.23)	2.63 (0.09)	5.60 (0.20)	2.72 (0.17)	5.37 (0.17)
Heart rate (beat min^{-1})	164.3 (10.7)	167.4 (12.0)	161.7 (10.7)	168.6 (13.7)	161.4 (11.6)
Cardiac output (litre min^{-1})	3.39 (0.39)	3.84 (0.49)	3.33 (0.30)	3.87 (0.51)	3.41 (0.27)
Mean arterial pressure (mm Hg)	134.6 (7.4)	**124.8 (7.9)	135.3 (7.9)	**125.4 (8.3)	133.1 (7.4)
Colonic blood flow (ml min^{-1} 100 g^{-1})	34.3 (1.7)	***25.7 (1.6)	36.8 (2.0)	***26.4 (1.2)	34.7 (1.9)
Colonic vascular resistance (unit)	3.97 (0.26)	*4.99 (0.50)	3.75 (0.31)	*4.82 (0.39)	3.91 (0.33)

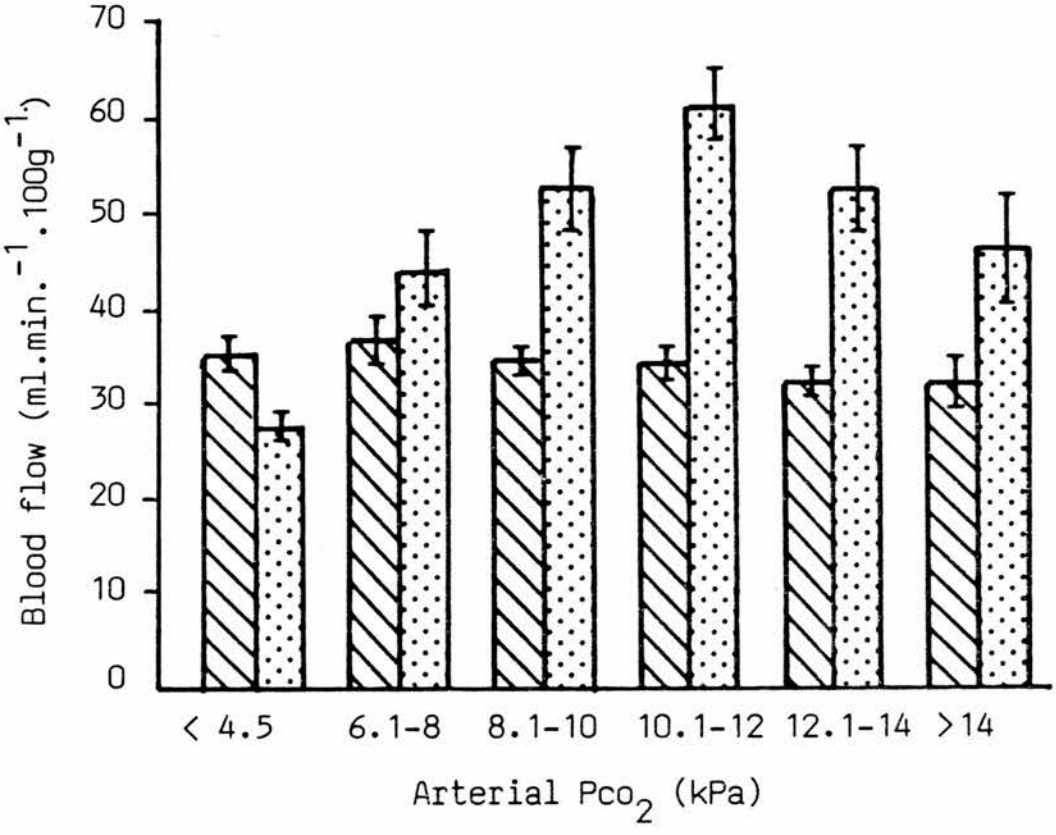
*$p < 0.05$)
**$p < 0.02$) Significance of differences between values at hypocapnia compared with preceding and subsequent values at normocapnia
***$p < 0.01$)

TABLE 5.2 Mean (sem) colonic blood flow, vascular resistance and oxygen consumption during acute changes in arterial carbon dioxide tension in the 23 animals in Group 1. (n = number of experiments).

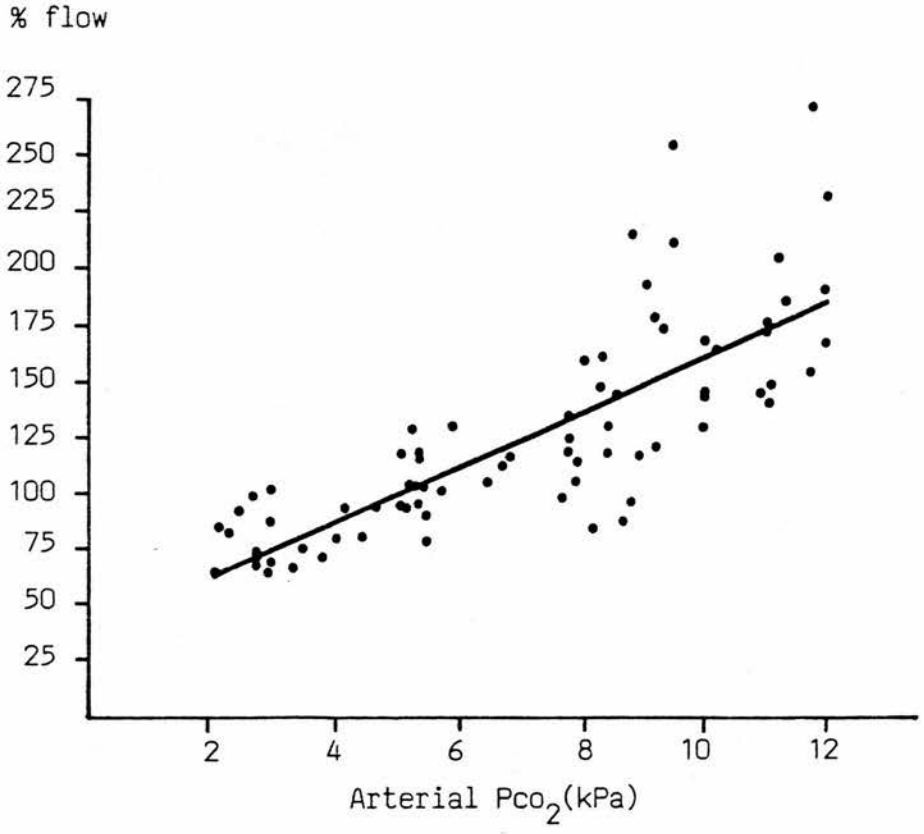
P_aCO_2 range (kPa)		Arterial PCO_2 (kPa)	Colonic blood flow (ml min^{-1} 100 g^{-1})	Colonic vascular resistance (unit)	Colonic oxygen consumption (ml min^{-1} 100 g^{-1})	n
< 4.5	Control	5.28 (0.09)	35.9 (1.6)	4.45 (0.28)	1.40 (0.07)	20
			p < .0005	p < 0.01	n.s.	
	Test	3.07 (0.12)	28.0 (1.4)	5.17 (0.27)	1.38 (0.10)	
6.1 - 8	Control	5.31 (0.18)	37.5 (2.1)	3.60 (0.29)	1.17 (0.09)	10
			p < 0.01	p < 0.01	n.s.	
	Test	7.37 (0.19)	44.7 (3.8)	3.14 (0.24)	1.38 (0.13)	
8.1 - 10	Control	5.24 (0.07)	35.2 (1.2)	3.97 (0.21)	1.37 (0.11)	19
			p < 0.0005	p < 0.001	p < 0.02	
	Test	9.09 (0.14)	53.2 (4.4)	2.88 (0.27)	2.24 (0.39)	
10.1 - 12	Control	5.28 (0.11)	34.9 (1.7)	3.87 (0.26)	1.35 (0.16)	13
			p < 0.0005	p < 0.001	p < 0.01	
	Test	11.34 (0.16)	62.2 (3.7)	2.14 (0.18)	2.17 (0.25)	
12.1 - 14	Control	5.32 (0.14)	33.0 (1.4)	4.19 (0.34)	1.53 (0.12)	11
			p < 0.0005	p < 0.001	p < 0.02	
	Test	12.80 (0.17)	53.5 (4.5)	2.58 (0.31)	2.34 (0.32)	
> 14	Control	5.33 (0.16)	33.0 (2.8)	4.52 (0.60)	1.32 (0.19)	6
			p < 0.02	p < 0.01	n.s.	
	Test	15.57 (0.44)	47.0 (5.6)	2.88 (0.43)	2.21 (0.58)	

TABLE 5.3 Mean (sem) heart rate, mean arterial pressure and cardiac output during acute changes in arterial carbon dioxide tension in the 23 animals in Group 1. (n = number of experiments).

P_aCO_2 range (kPa)		Arterial PCO_2 (kPa)	Heart rate (beat min^{-1})	Mean arterial pressure (mm Hg)	Cardiac output (litre min^{-1})	n
< 4.5	Control	5.28 (0.09)	153.5 (7.0)	141.1 (3.3)	2.57 (0.10)	20
			p < .005	**p < 0.01**	**n.s.**	
	Test	3.07 (0.12)	160.4 (7.6)	135.2 (4.5)	2.47 (0.11)	
6.1 - 8	Control	5.31 (0.18)	152.1 (9.3)	131.7 (5.7)	2.65 (0.14)	10
			n.s.	**n.s.**	**n.s.**	
	Test	7.37 (0.19)	147.9 (7.0)	131.3 (6.1)	2.63 (0.13)	
8.1 - 10	Control	5.24 (0.07)	158.4 (6.7)	142.0 (2.9)	3.01 (0.25)	19
			p < 0.0005	**p < 0.002**	**n.s.**	
	Test	9.09 (0.14)	145.2 (5.8)	133.3 (4.3)	2.92 (0.20)	
10.1 - 12	Control	5.28 (0.11)	148.1 (8.1)	140.5 (5.1)	2.72 (0.14)	13
			p < 0.0005	**p < 0.0005**	**n.s.**	
	Test	11.34 (0.16)	130.8 (5.9)	126.7 (5.7)	2.86 (0.16)	
12.1 - 14	Control	5.32 (0.14)	163.2 (10.4)	137.9 (7.5)	2.51 (0.36)	11
			p < 0.0005	**p < 0.005**	**n.s.**	
	Test	12.80 (0.17)	144.5 (8.8)	124.5 (6.0)	2.59 (0.29)	
> 14	Control	5.33 (0.16)	175.0 (18.4)	139.3 (9.2)	2.15 (0.18)	6
			p < 0.002	**p < 0.0005**	**n.s.**	
	Test	15.57 (0.44)	159.2 (17.3)	124.8 (8.2)	2.45 (0.27)	

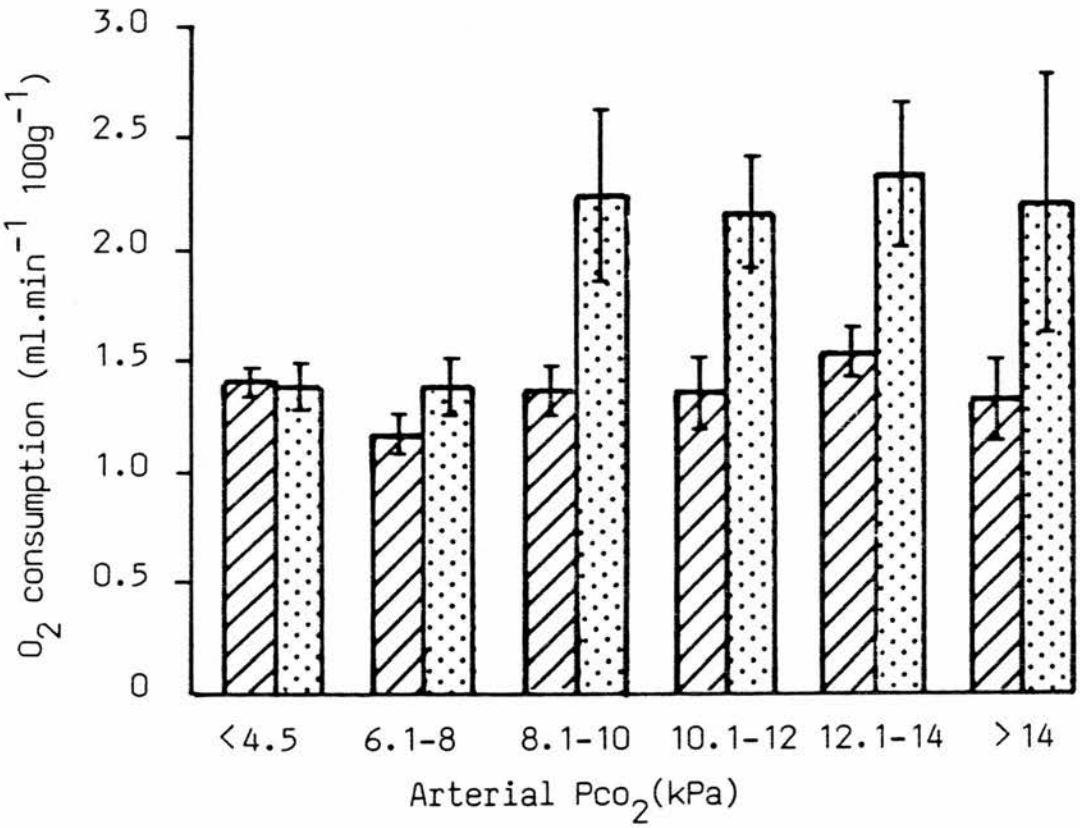


Effects of acute alterations in P_aCO_2 on colonic blood flow in 23 dogs. Cross-hatched blocks represent the mean control values at normocapnia immediately before each alteration in P_aCO_2. The stippled blocks represent mean values after the change had been made to a P_aCO_2 in the ranges shown on the horizontal axis. Bars represent sem. Significance values shown in Table 5.2.



Relationship between P_aCO_2 between 2 and 12 kPa and percentage increase in colonic blood flow relative to values at normocapnia (74 values from 35 dogs). The equation of the regression line is:

$y = 12.10x + 35.05 \qquad r = 0.80 \qquad p < 0.001$



Effects of acute alterations in P_aCO_2 on colonic oxygen consumption in 23 dogs. Cross-hatched blocks represent the mean control values at normocapnia immediately before each alteration in P_aCO_2. The stippled blocks represent mean values after the change had been made to a P_aCO_2 in the ranges shown on the horizontal axis. Bars represent sem. Significance values shown in Table 5.2.

tensions of between 2 and 12 kPa (Figure 5.2), although above 12 kPa the relationship was no longer linear.

Heart rate and mean arterial pressure decreased when P_aCO_2 exceeded 8 kPa, but there were no significant changes in cardiac output irrespective of the P_aCO_2 (Table 5.3). Because of the changes in arterial pressure, the effect of hypercapnia on colonic vascular resistance (Table 5.2) was proportionately less than that on colonic blood flow. Pulmonary arterial pressure increased when P_aCO_2 exceeded 14 kPa, and central venous pressure increased at P_aCO_2 values in excess of 12 kPa. Arterial pH changes were commensurate with those of P_aCO_2, and there were no significant alterations in base excess.

Colonic oxygen consumption increased significantly at P_aCO_2 values in excess of 8 kPa and up to 14 kPa (Figure 5.3; Table 5.2).

[**5.3.2**] Acute hypocapnia - Group 2

Hypocapnia to a mean arterial P_{CO_2} of 2.52 ± 0.16 kPa (normocapnic P_{CO_2} 5.20 ± 0.07 kPa) resulted in a significant increase in heart rate, but significant decreases in mean arterial pressure and total peripheral resistance (Table 5.4). There was a small but statistically significant increase in cardiac output. Colonic blood flow decreased by 23.2%, and there was a small but statistically insignificant increase in colonic vascular resistance. There was no significant alteration in colonic oxygen consumption.

There were large increases in lactate concentrations in arterial, mixed venous and colonic venous samples in response to hypocapnia (Table 5.5). Pyruvate concentrations also tended to increase, although none of the changes was statistically significant. However, the lactate/pyruvate ratio increased significantly in blood

TABLE 5.4 Effects of acute hypocapnia. Values from the 23 dogs in Group 2 expressed as mean (sem).

	Normocapnia	p	Hypocapnia
Arterial carbon dioxide tension (kPa)	5.20 (0.07)		2.52 (0.16)
Heart rate (beat min^{-1})	145.8 (5.1)	< 0.001	155.5 (5.4)
Mean systemic arterial pressure (mm Hg)	138.0 (5.4)	< 0.005	120.3 (6.2)
Cardiac output (litre min^{-1})	4.99 (0.28)	< 0.05	5.31 (0.27)
Total peripheral resistance (unit)	30.6 (2.2)	< 0.01	25.5 (1.9)
Total oxygen consumption (ml min^{-1})	204.4 (14.5)	n.s.	224.3 (20.0)
Colon blood flow (ml min^{-1} 100 g^{-1})	41.4 (1.6)	< 0.0005	31.8 (2.3)
Colon vascular resistance (unit)	3.48 (0.21)	n.s.	3.91 (0.31)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.13 (0.16)	n.s.	1.30 (0.22)

TABLE 5.5 Effects of acute hypocapnia on blood lactate and pyruvate concentrations. Values from 11 dogs in Group 2 expressed as mean (sem).

	Normocapnia	p	Hypocapnia
Arterial lactate concentration (μmol litre^{-1})	692.9 (74.5)	< 0.02	1202.9 (215.7)
Arterial pyruvate concentration (μmol litre^{-1})	87.0 (8.2)	n.s.	89.7 (10.8)
Arterial lactate/pyruvate ratio	8.20 (1.02)	< 0.02	13.41 (1.74)
Mixed venous lactate concentration (μmol litre^{-1})	848.8 (148.2)	< 0.05	1352.5 (180.6)
Mixed venous pyruvate concentration (μmol litre^{-1})	72.9 (7.9)	n.s.	94.9 (14.5)
Mixed venous lactate/pyruvate ratio	10.22 (1.25)	< 0.02	13.93 (1.76)
Colon lactate concentration (μmol litre^{-1})	782.5 (123.3)	< 0.005	1173.8 (117.5)
Colon pyruvate concentration (μmol litre^{-1})	79.0 (9.1)	n.s.	83.0 (8.8)
Colon lactate/pyruvate ratio	10.27 (1.40)	< 0.05	13.73 (0.99)

from all three sources during the period of acute hypocapnia. There were no significant differences between lactate or pyruvate concentrations, or in lactate/pyruvate ratio, between arterial, mixed venous and colonic venous samples either at normocapnia or hypocapnia.

[5.3.3] Acute hypercapnia - Group 2

An increase in arterial P_{CO_2} from 5.35 ± 0.08 kPa to 11.33 ± 0.39 kPa resulted in no significant changes in heart rate, mean arterial pressure, or total peripheral resistance (Table 5.6). There was a highly significant increase in cardiac output. Colonic blood flow increased significantly, and this change was accompanied by a significant decrease in colonic vascular resistance. There was no significant alteration in colonic oxygen consumption.

There were significant decreases in lactic acid concentrations in arterial, mixed venous and colonic venous blood in response to hypercapnia (Table 5.7). In addition, there appeared to be decreases in pyruvic acid concentrations in blood from all three sources, although only the changes in venous pyruvate concentrations were statistically significant. The ratios of lactate/pyruvate in blood from all three sampling sites did not change significantly in response to hypercapnia, although there was a consistent downward trend. The pyruvate concentration in mixed venous blood during hypercapnia was significantly ($p < 0.05$) lower than that in arterial blood. Although the mean value of pyruvate in colonic venous blood was identical to that in mixed venous blood, the scatter of values was greater, and the difference between pyruvate concentrations in arterial and colonic venous blood was not statistically significant.

TABLE 5.6 Effects of acute hypercapnia. Values from the 23 dogs in Group 2 expressed as mean (sem).

	Normocapnia	p	Hypercapnia
Arterial carbon dioxide tension (kPa)	5.35 (0.08)		11.33 (0.39)
Heart rate (beat min^{-1})	137.4 (5.6)	n.s.	136.5 (4.7)
Mean systemic arterial pressure (mm Hg)	142.1 (4.2)	n.s.	137.2 (5.2)
Cardiac output (litre min^{-1})	4.36 (0.27)	< 0.0001	5.46 (0.28)
Total peripheral resistance (unit)	32.7 (2.5)	n.s.	27.6 (1.8)
Total oxygen consumption (ml min^{-1})	201.9 (14.9)	n.s.	240.8 (33.4)
Colon blood flow (ml min^{-1} 100 g^{-1})	42.0 (1.7)	< 0.0001	62.1 (3.5)
Colon vascular resistance (unit)	3.51 (0.21)	< 0.0001	2.30 (0.14)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.14 (0.12)	n.s.	1.01 (0.22)

TABLE 5.7 Effects of acute hypercapnia on blood lactate and pyruvate concentrations. Values from 11 dogs in Group 2 expressed as mean (sem).

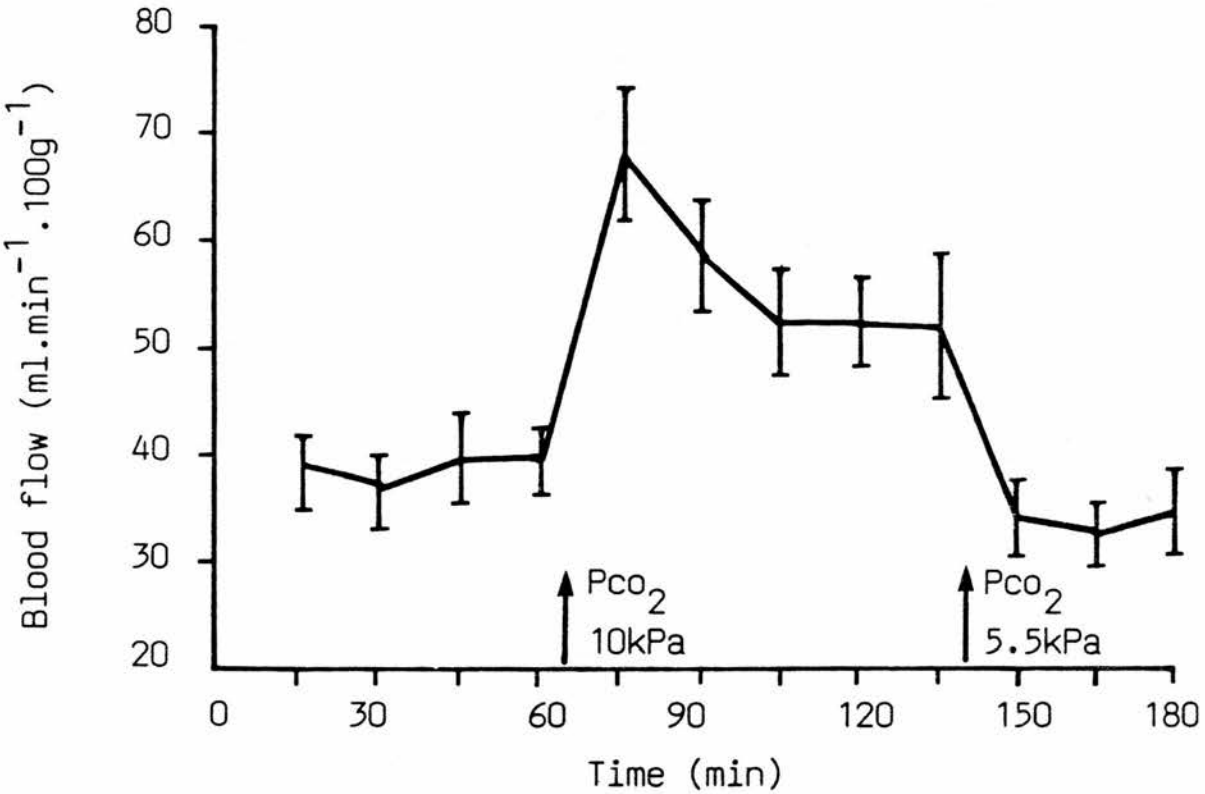
	Normocapnia	p	Hypercapnia
Arterial lactate concentration (μmol litre^{-1})	935.0 (178.4)	< 0.02	523.8 (89.7)
Arterial pyruvate concentration (μmol litre^{-1})	80.7 (13.3)	n.s.	74.9 (11.9)
Arterial lactate/pyruvate ratio	10.63 (1.53)	n.s.	7.26 (1.70)
Mixed venous lactate concentration (μmol litre^{-1})	750.0 (91.8)	< 0.05	473.8 (92.9)
Mixed venous pyruvate concentration (μmol litre^{-1})	81.8 (8.6)	< 0.005	58.3 (6.9)
Mixed venous lactate/pyruvate ratio	9.52 (0.97)	n.s.	8.67 (1.64)
Colon lactate concentration (μmol litre^{-1})	812.5 (99.6)	< 0.001	455.0 (63.8)
Colon pyruvate concentration (μmol litre^{-1})	73.9 (9.7)	< 0.05	58.3 (10.4)
Colon lactate/pyruvate ratio	12.04 (1.91)	n.s.	9.30 (1.35)

There were no significant differences in lactate concentration, or in lactate/pyruvate ratio, between arterial, mixed venous and colonic venous samples either at normocapnia or hypercapnia.

[5.3.4] Prolonged changes in P_aCO_2

The mean P_aCO_2 during prolonged hypercapnia was 9.67 $\pm$ 0.16 kPa Colonic blood flow increased significantly ($p < 0.001$) on induction of hypercapnia (Figure 5.4; Table 5.8), but decreased over the succeeding 30 min before plateauing at a value which remained significantly greater than the control flow at 60 min ($p < 0.05$), but significantly lower than the peak at 75 min ($p < 0.005$). Restoration of normocapnia resulted in a significant ($p < 0.005$) decrease in colonic blood flow to a value which was slightly, but not significantly, less than control. Mean arterial pressure decreased significantly ($p < 0.02$) on induction of hypercapnia. The changes in colonic vascular resistance which occurred at the beginning and the end of the period of hypercapnia were significant ($p < 0.01$).

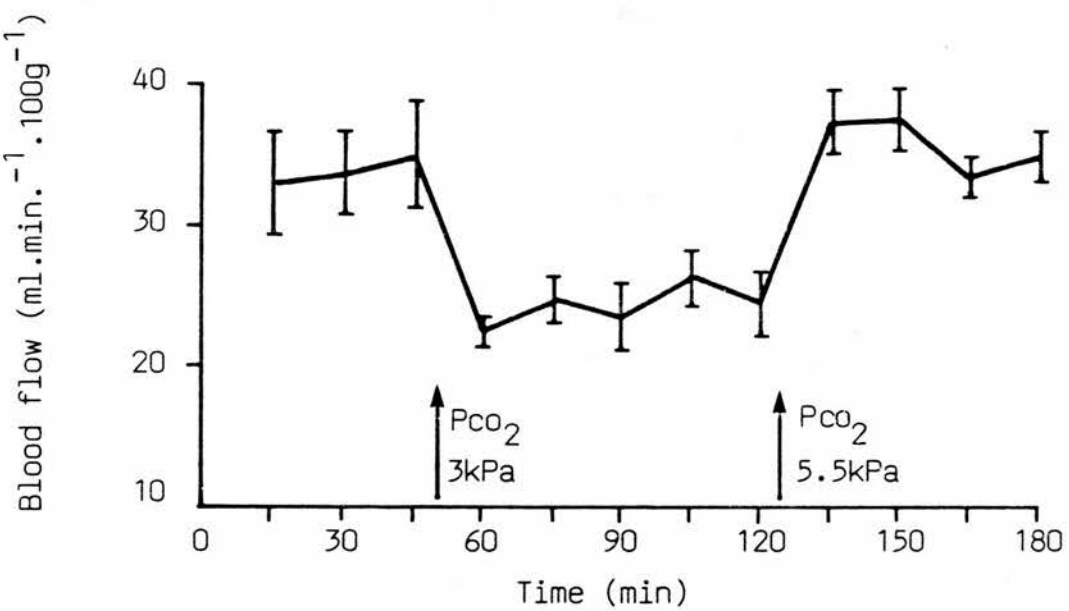
During prolonged hypocapnia, the mean P_aCO_2 was 3.07 $\pm$ 0.06 kPa. There were no significant differences in colonic blood flow after the initial decrease of 36% between 45 and 60 min (Figure 5.5; Table 5.9). Following restoration of normocapnia, colonic blood flow increased to values which did not differ significantly from the control measurements. There were no significant changes in mean arterial pressure, and the alterations in colonic vascular resistance mirrored those in colonic blood flow. The changes in both colonic parameters at the beginning and end of the period of hypocapnia were significant ($p < 0.005$).



Effects with time of prolonged hypercapnia on mean colonic blood flow in five dogs. P_aCO_2 was increased to approximately 10 kPa at 65 min, and returned to normal values at 140 min. Bars represent sem. Values shown in Table 5.8. Significance values detailed in text.

TABLE 5.8 Effects of prolonged hypercapnia on mean arterial pressure, colonic blood flow and colonic vascular resistance. Values are from five dogs, and are expressed as mean (sem).

Time	Arterial PCO_2 (kPa)	Mean arterial pressure (mm Hg)	Colonic blood flow (ml min^{-1} 100 g^{-1})	Colonic vascular resistance (unit)
15 min	5.65 (0.17)	135.8 (2.8)	39.0 (3.9)	3.60 (0.30)
30 min	5.52 (0.20)	130.8 (4.3)	36.8 (3.3)	3.65 (0.30)
45 min	5.25 (0.20)	128.4 (4.5)	39.6 (4.1)	3.40 (0.41)
60 min	5.49 (0.10)	132.8 (4.5)	39.6 (3.0)	3.46 (0.37)
Hypercapnia				
75 min	9.81 (0.55)	124.4 (5.5)	68.2 (6.5)	1.93 (0.27)
90 min	9.97 (0.39)	126.2 (8.6)	58.6 (5.1)	2.26 (0.31)
105 min	9.65 (0.16)	127.8 (7.0)	52.4 (5.0)	2.56 (0.33)
120 min	9.41 (0.32)	124.8 (6.9)	52.6 (4.2)	2.47 (0.30)
135 min	9.49 (0.31)	127.2 (6.4)	52.2 (7.0)	2.63 (0.40)
Normocapnia				
150 min	5.49 (0.23)	130.2 (9.0)	34.2 (3.6)	4.00 (0.54)
165 min	5.39 (0.10)	136.4 (3.0)	32.6 (3.3)	4.32 (0.35)
180 min	5.31 (0.08)	133.8 (5.0)	34.8 (3.9)	4.00 (0.38)



Effects with time of prolonged hypocapnia on mean colonic blood flow in five dogs. P_aCO_2 was decreased to approximately 3 kPa at 50 min, and returned to normal values at 125 min. Bars represent sem. Values shown in Table 5.9. Significance values detailed in text.

TABLE 5.9 Effects of prolonged hypocapnia on mean arterial pressure, colonic blood flow and colonic vascular resistance. Values are from five dogs, and are expressed as mean (sem).

Time	Arterial PCO_2 (kPa)	Mean arterial pressure (mm Hg)	Colonic blood flow (ml min^{-1} 100 g^{-1})	Colonic vascular resistance (unit)
15 min	5.39 (0.10)	135.4 (3.1)	33.0 (3.7)	4.27 (0.39)
30 min	5.29 (0.08)	134.8 (5.0)	33.8 (3.0)	4.08 (0.30)
45 min	5.49 (0.15)	134.4 (4.0)	35.0 (3.8)	3.98 (0.35)
Hypocapnia				
60 min	3.20 (0.20)	131.2 (5.5)	22.4 (1.2)	5.88 (0.15)
75 min	3.01 (0.20)	127.8 (5.0)	24.8 (1.7)	5.24 (0.39)
90 min	3.01 (0.07)	130.2 (5.0)	23.6 (2.5)	5.80 (0.76)
105 min	3.07 (0.08)	129.2 (4.9)	26.4 (2.0)	4.96 (0.21)
120 min	3.07 (0.14)	129.4 (4.6)	24.6 (2.2)	5.44 (0.52)
Normocapnia				
135 min	5.20 (0.19)	136.8 (3.8)	37.4 (2.3)	3.72 (0.28)
150 min	5.57 (0.22)	141.8 (3.5)	37.6 (2.1)	3.83 (0.25)
165 min	5.52 (0.30)	140.2 (4.2)	33.4 (1.6)	4.37 (0.29)
180 min	5.33 (0.12)	139.0 (6.5)	34.8 (1.8)	4.06 (0.35)

[5.4] DISCUSSION

[5.4.1] Haemodynamic changes

The haemodynamic responses to alterations in blood carbon dioxide tension are complex, and represent a balance between the direct effects of pH changes induced by CO_2 and secondary effects on the central and autonomic nervous systems.

Using an *in vitro* preparation of the cat papillary muscle, it has been demonstrated that hypercapnia reduces all indices of myocardial performance, both under isotonic and isometric conditions (Pannier and Leusen, 1968). Conversely, hypocapnia enhances myocardial performance. However, when the pH is kept constant during hypercapnia by addition of sodium bicarbonate to the perfusate, the depressant effect of carbon dioxide is not seen, suggesting that it is the change in pH rather than the alteration in P_{CO_2} which produces the effect (Pannier and Brutsaert, 1968; Pannier and Leusen, 1968). The myocardial depression induced by CO_2 is of relatively short duration, and a significant degree of recovery is seen over a period of 1 hr (Foëx and Fordham, 1972). This has been attributed to intracellular buffering of the increased hydrogen ion concentration associated with hypercapnia.

Hypercapnia is a potent stimulus for the peripheral chemoreceptors and for the vasomotor centres of the medulla (Tenney, 1960). The stimulation induced results in an increase in sympathetic nervous activity and in an increased secretion of catecholamines (Morris and Millar, 1962a; Tenney, 1956). There is a near linear relationship between pH and total plasma catecholamine concentrations, and the increases in sympathetic activity and catecholamine concentrations result in a positive inotropic and chronotropic effect on the

myocardium (Foëx, 1980). In the presence of hypocapnia, postganglionic sympathetic activity is reduced (Moster et al., 1969), and plasma catecholamine concentrations are very low (Morris and Millar, 1962a; Morris and Millar, 1962b). In the present study, acute hypocapnia resulted in a decrease in mean arterial pressure, and increases in heart rate in both groups of dogs, and in cardiac output in one group. The latter changes may have been the result of baroreceptor stimulation. Hypercapnia resulted in an increase in cardiac output, with no significant decreases in mean arterial pressure or heart rate in the animals in Group 2, and a decrease in both arterial pressure and heart rate, but no significant increase in cardiac output, in Group 1.

The direct effect of hypercapnia on the peripheral vessels is one of depression of myogenic activity. The vasodilator effect of CO_2 is particularly apparent in the cerebral circulation. In the dog, maximal vasodilatation occurs at a P_aCO_2 of approximately 10.5 kPa (Harper and Glass, 1965). Blood flow tends to return to normal values if hypercapnia is prolonged. The effect of CO_2 on cerebral vessels is believed to be direct, as at a constant P_{CO_2}, variations in arterial pH do not produce significant alterations in blood flow. Hypocapnia produces cerebral vasoconstriction, and between an arterial P_{CO_2} of 2.7 kPa and 10.7 kPa, there is a linear relationship between P_aCO_2 and cerebral blood flow (Reivich, 1964). In the coronary circulation, hypercapnia results in vasodilatation (Ledingham et al., 1970), and hypocapnia in vasoconstriction (Vance, Brown and Smith, 1973). During prolonged hypercapnia, the effect of CO_2 on coronary artery flow diminishes, but the reduction in flow associated with prolonged hypocapnia is maintained. The reduction in coronary artery flow in the

presence of hypocapnia is associated with increased myocardial oxygen extraction, although myocardial oxygen consumption remains unaltered. The effects of CO_2 on other tissues vary, depending upon the balance between the direct effects of CO_2 and the opposing effects of the sympathetic nervous system. Blood flow in skeletal muscle increases in response to hypocapnia, and it is thought that this is a direct vasodilator response (Burnum, Hickam and McIntosh, 1954; Roddie, Shepherd and Whelan, 1957). Changes in total peripheral resistance therefore represent the average of various responses in the body.

In the present studies, total peripheral resistance decreased by 15 - 16% in response to both hypocapnia and hypercapnia. Colonic vascular resistance increased significantly in response to hypocapnia in the Group 1 animals, although the increase was not statistically significant in Group 2. All animals demonstrated a marked decrease in colonic vascular resistance in response to hypercapnia. Colonic blood flow invariably decreased during hypocapnia, and increased during hypercapnia, although the increases were less marked when P_aCO_2 exceeded 12 kPa. The smaller increases at very high P_aCO_2 values were a result of a diminished effect on the colonic vessels rather than a reflection of myocardial depression, as the effect of CO_2 on the colonic vascular resistance was reduced while cardiac output remained unaltered. During prolonged exposure to hypercapnia, colonic blood flow decreased over a 30 min period from the initially elevated level. This decrease was associated with an increase in colonic vascular resistance while mean arterial pressure remained stable, and may reflect an intracellular compensatory mechanism similar to that proposed within the myocardium (<u>vide supra</u>). As has been reported in other tissues, the reduction in blood flow associated with hypocapnia

was maintained in the colon over a 60 min period.

Cardiovascular depression due to raised intrathoracic pressure might have been a contributory factor in respect of the reduction in colonic blood flow which occurred in response to hypocapnia. Little and Smith (1964) and Scheuer (1968) found that mean arterial pressure decreased during hyperventilation which achieved an arterial or alveolar P_{CO_2} of approximately 2 kPa, although Cullen, Eger and Gregory (1969) and Marshall and others (1971) found no differences in cardiac index or total peripheral resistance between normocapnic and hypocapnic states, although in these studies the degree of hypocapnia was less (P_aCO_2 approximately 3 kPa). Richardson, Wasserman and Patterson (1961) have suggested that the circulatory changes associated with hyperventilation are related to the extent of reduction of P_aCO_2, rather than the mechanical effects of hyperventilation. The findings of the present study tend to substantiate this view. Mean arterial pressure, cardiac output, colonic blood flow and colonic vascular resistance were essentially unchanged during normocapnia whether or not hyperventilation was applied (Table 5.1), demonstrating that the alterations in these parameters which occurred during hypocapnia were not related to the pattern of mechanical ventilation.

[**5.4.2**] Colonic oxygen consumption

Colonic oxygen consumption was not affected significantly by hypocapnia. There was no alteration in response to hypercapnia in the animals in Group 2, although dogs in Group 1 displayed a significant increase in colonic oxygen consumption at P_aCO_2 values between 8 and 14 kPa. This may have been related to an increased metabolic rate resulting from the elevated sympathetic nervous system activity ass-

ociated with an elevation in P_{CO_2} (Tenney, 1960). Ledingham and others (1971) found that myocardial oxygen consumption was reduced by hypercapnia, but this reduction was associated with a reduction in cardiac work. In contrast, cerebral oxygen consumption is decreased by extreme hypocapnia (P_aCO_2 1.5 kPa), and this reduction is thought to represent a conversion to anaerobic metabolism resulting from cellular hypoxia produced by a greatly reduced cerebral blood flow (Harp and Wollman, 1973).

[**5.4.3**] Lactate and pyruvate concentrations

The major metabolic pathway of glucose in cells is via cleavage to trioses in the Embden-Myerhof pathway, resulting in the production of pyruvate. In the presence of oxygen, pyruvate is converted to acetyl Coenzyme A (acetyl-CoA), and enters the citric acid cycle. A proportion of pyruvate is converted into lactate, as shown by the equation:

[12] $$\text{Pyruvate} + \text{NADH} + H^+ \overset{\text{LDH}}{\rightleftharpoons} \text{Lactate} + NAD^+$$

where LDH = lactate dehydrogenase, H^+ = hydrogen ion, NAD^+ = nicotinamide adenine dinucleotide, and NADH = dihydronicotinamide adenine dinucleotide.

Normally, this proportion is small. The plasma lactate concentration may be raised without a shift in the equilibrium of equation **[12]** if the concentration of pyruvate increases, or, in the presence of inadequate oxygen, by excess formation of NADH (Huckabee, 1958). The latter results in an increase in the lactate/pyruvate ratio. Equation **[12]** may be rearranged in the following manner:

[13] $$\frac{\text{Lactate}}{\text{Pyruvate}} = K \frac{\text{NADH} \times H^+}{NAD^+}$$

An increased lactate pyruvate ratio in blood can therefore be interpreted as a reflection of an increased $NADH/NAD^+$ ratio in the mitochondria (Cohen, 1972). It has been claimed (Huckabee, 1958) that an elevated lactate/pyruvate ratio is a sensitive index of cellular hypoxia, although Cohen drew attention to a number of objections to this view and noted that excess lactate concentrations could occur in the absence of mitochondrial hypoxia. Weil and Afifi (1970) maintained that, in the presence of tissue hypoxia, the lactate concentration itself may be a more accurate indicator of the degree of hypoxia than the lactate/pyruvate ratio.

During aerobic glycolysis, the production of adenosine triphosphate (ATP) is 19 times greater than that under anaerobic conditions. The reduction in ATP production results in a positive feedback by increasing the release of the enzyme phosphofructokinase, which increases conversion of fructose-6-phosphate to fructose-1,6-diphosphate within the Embden-Myerhof pathway (Duffy, Nelson and Lowry, 1972). More pyruvate is formed, and lactate production is increased. Phosphofructokinase is sensitive to pH changes, and alkalosis markedly increases the production of lactate (Scheuer and Berry, 1967).

In the present studies, concentrations of lactate in arterial, mixed venous and colonic venous blood were significantly increased in the presence of hypocapnia. Lactate/pyruvate ratios in blood from all three sampling sites were also increased. However, as neither the concentration of lactate nor the lactate/pyruvate ratio in colonic venous blood differed significantly from the corresponding values in

arterial or mixed venous blood, and as the lactate concentration did not exceed the upper limit of the normal range (1800 μmol litre^{-1}), there was no evidence to suggest that a significant degree of anaerobic metabolism occurred in the colon in association with the reduced blood flow resulting from hypocapnia. Hypercapnia resulted in decreases in lactate concentrations, and a tendency to lower lactate/pyruvate ratios. It is likely that these changes reflect the effects discussed above of pH on the Embden-Myerhof pathway. In retrospect, correction of the pH to normal during hypocapnia and hypercapnia and repetition of the measurements of lactate and pyruvate might have been of interest.

[**5.4.4**] Clinical significance

The practice of deliberate hyperventilation during anaesthesia is common during surgery involving the abdominal contents. In addition, mechanical ventilation is employed in intensive care units, where hypocapnia is usually sought in order to minimise respiratory drive and reduce requirements for sedation. The results of these studies demonstrate that hypocapnia reduces blood flow to the colon. While no evidence was found of anaerobic metabolism, it should be borne in mind that these experiments were undertaken on the normal colon. If blood flow to an anastomosis is already compromised by surgical factors, the additional reduction resulting from hypocapnia might result in a reduced oxygen supply to an anastomosis, and impair its healing. There appear to be theoretical grounds for the employment of normocapnic ventilation in such patients.

Conversely, the possibility arises that minor degrees of hypoventilation in the post-operative period, e.g. due to the administr-

ation of opioids, may improve blood flow to an anastomosis, and could be of benefit provided that adequate oxygenation of the arterial blood is maintained.

An anastomotic suture line may be relatively hypoxic due to impairment of its blood supply from mechanical factors. In the presence of hypoxia, the colonic vascular resistance increases by approximately 30% (Gilmour, Aitkenhead and Ledingham, 1980), in contrast to the maximal vasodilatation which occurs in the coronary and cerebral vascular beds (Roberts, 1980). Thus while the combination of local hypoxia and arterial hypercapnia may result in a reduction of blood flow to the hypoxic area in myocardium and brain, and conversely hypocapnia may improve perfusion of the affected area, the same arguments may not apply to the colon.

CHAPTER SIX

THE EFFECTS OF MODERATE HYPOVOLAEMIA

[6.1] INTRODUCTION

Moderate to severe haemorrhage (30% of blood volume) has been shown to reduce mesenteric blood flow by up to 75% (Matthews and Parks, 1976), in association with marked systemic haemodynamic changes. It would be unusual to find untreated haemorrhage to this degree in patients undergoing colonic surgery. However, lesser degrees of haemorrhage are not uncommon, and are known to be associated with an increased risk of anastomotic disruption (Schrock, Deveney and Dunphy, 1973). As the splanchnic circulation is one of the principal sources of autotransfusion in hypovolaemia (Ganong, 1979), it is likely that mild haemorrhage might reduce colonic blood flow as part of the body's attempt to compensate for the reduced blood volume in order to maintain systemic arterial blood pressure and to preserve perfusion of more vital organs. In patients undergoing colonic anastomosis, mild hypovolaemia during surgery or in the post-operative period could thus reduce oxygen delivery to the anastomotic site, impairing healing and increasing the risk of anastomotic breakdown (see Chapter Two).

The purpose of the investigation described in this chapter was to study the effects of moderate hypovolaemia on colonic blood flow and colonic oxygen consumption in the animal model. The degree of hypovolaemia selected was one which produced no gross changes in the cardiovascular parameters commonly monitored in clinical practice.

[6.2] METHODS

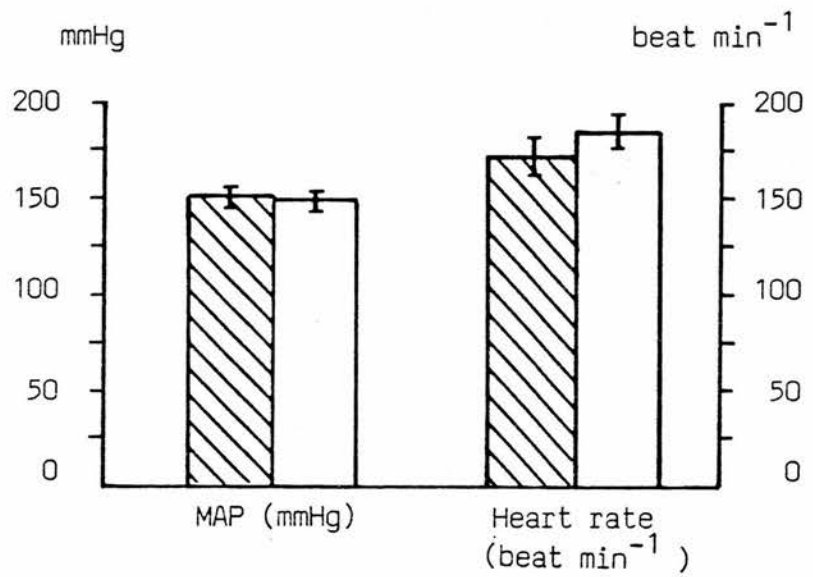
Nine greyhounds, of weight ranging from 20 to 33 kg, were studied in this series of experiments. Following laparotomy and placement of catheters as described in Chapter Four, a period of 60 min was allowed for stabilisation. During this period, the full set of cardiovascular and biochemical measurements were made every 15 min.

Immediately after the last of these sets of measurements had been completed, an estimated 15% of the dog's blood volume was removed by passive bleeding from the aortic catheter of 12 ml kg^{-1}. Blood volume was assumed to be approximately 80 ml kg^{-1} (Stewart et al., 1950). Haemorrhage occurred at a reasonably uniform rate, and the calculated volume was removed in approximately 20 min. The shed blood was collected in a calibrated blood transfusion bottle to which had been added 5000 units of heparin. All measurements were repeated 5 min after haemorrhage was complete, and 15 and 30 min later. The animal was then retransfused with its own blood over a 20 min period. Following transfusion, all measurements were repeated at 5 min, and then at 15 min intervals for 1 hr.

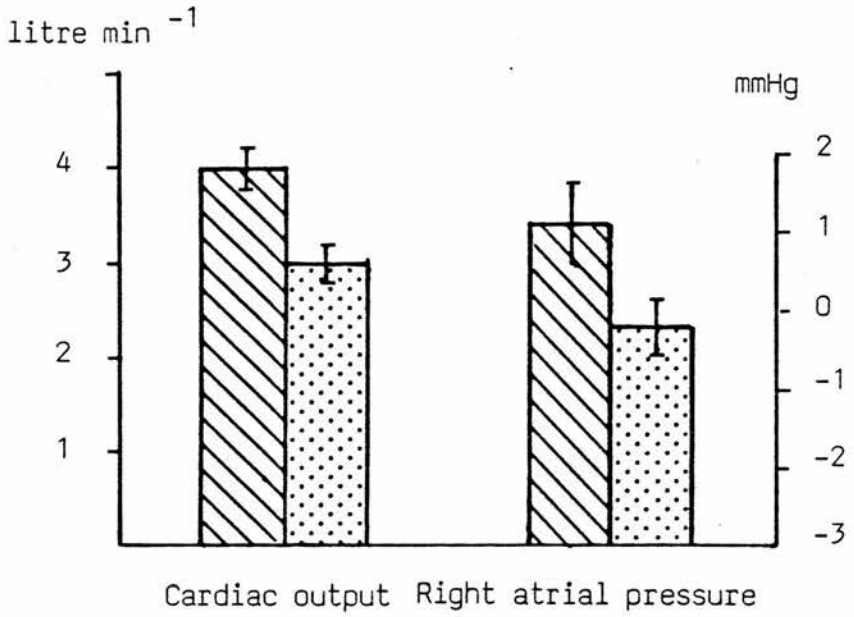
[6.3] RESULTS

[6.3.1] Effects of haemorrhage

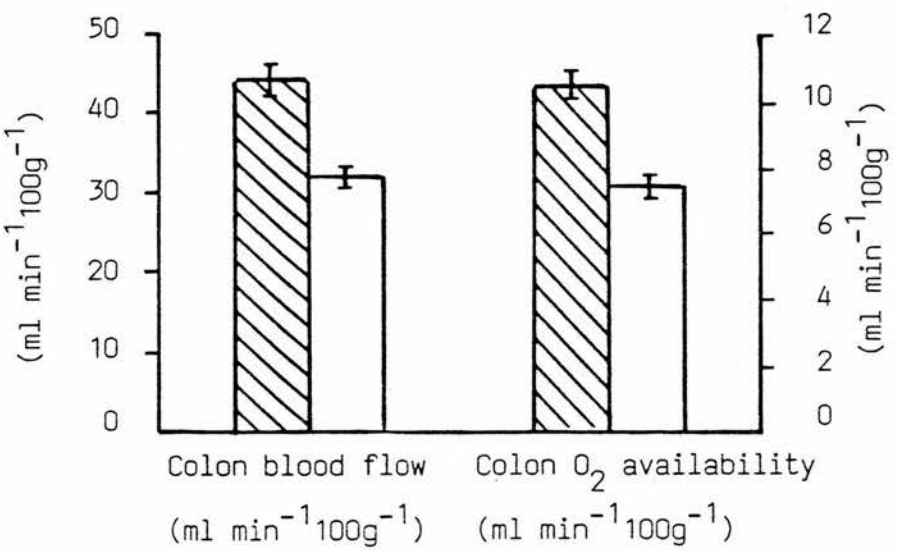
Mean systemic arterial pressure did not alter significantly in response to haemorrhage (Figure 6.1). The increase in heart rate which accompanied haemorrhage was small (mean 6.9%) although statistically significant ($p < 0.002$). There was, however, a decrease of 25.5% in cardiac output ($p < 0.0005$) and a sizeable decrease in right atrial pressure ($p < 0.002$) (Figure 6.2).



Mean arterial pressure (MAP) and heart rate before (cross-hatched) and after (open) haemorrhage of 15% of blood volume in nine dogs. Bars represent sem. No significant differences.



Cardiac output and right atrial pressure before (cross-hatched) and after (stippled) haemorrhage of 15% of blood volume in nine dogs. Bars represent sem. Significance values in text.

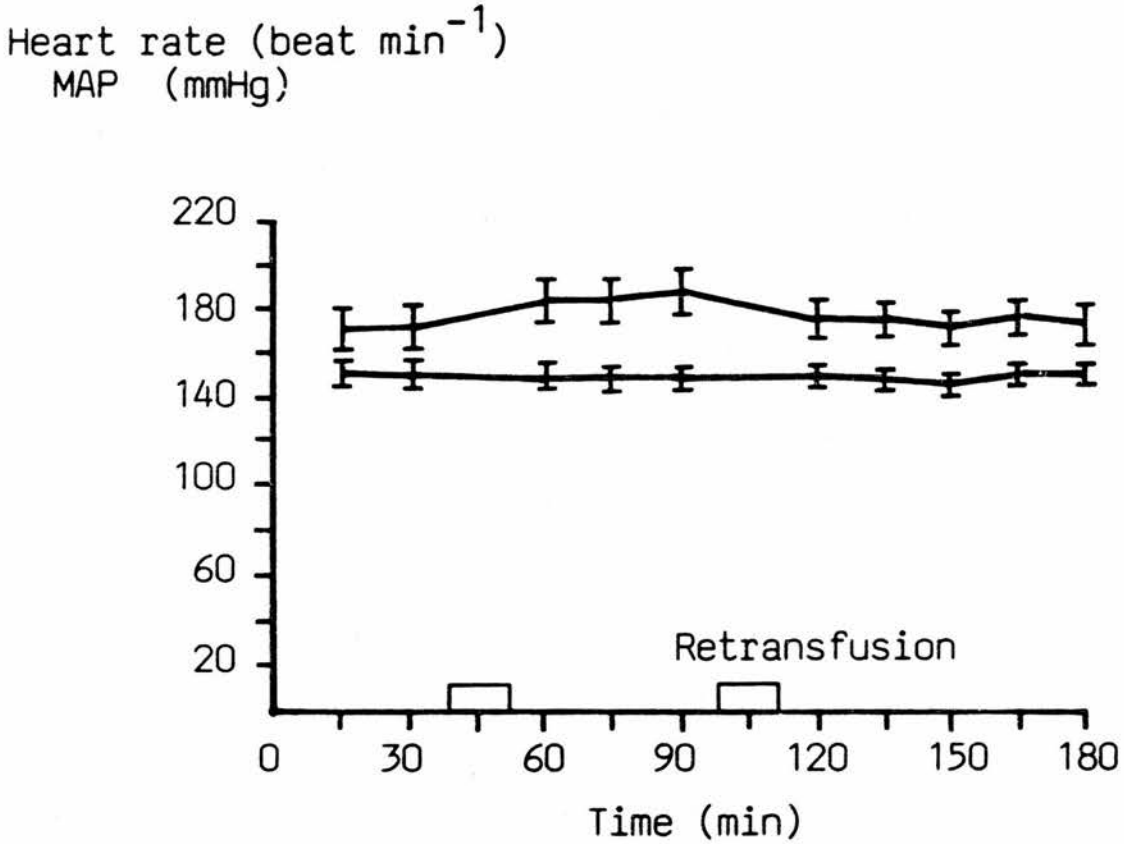


Colonic blood flow and colonic oxygen availability before (cross-hatched) and after (open) haemorrhage of 15% of blood volume in nine dogs. Bars represent sem. Significance values in text.

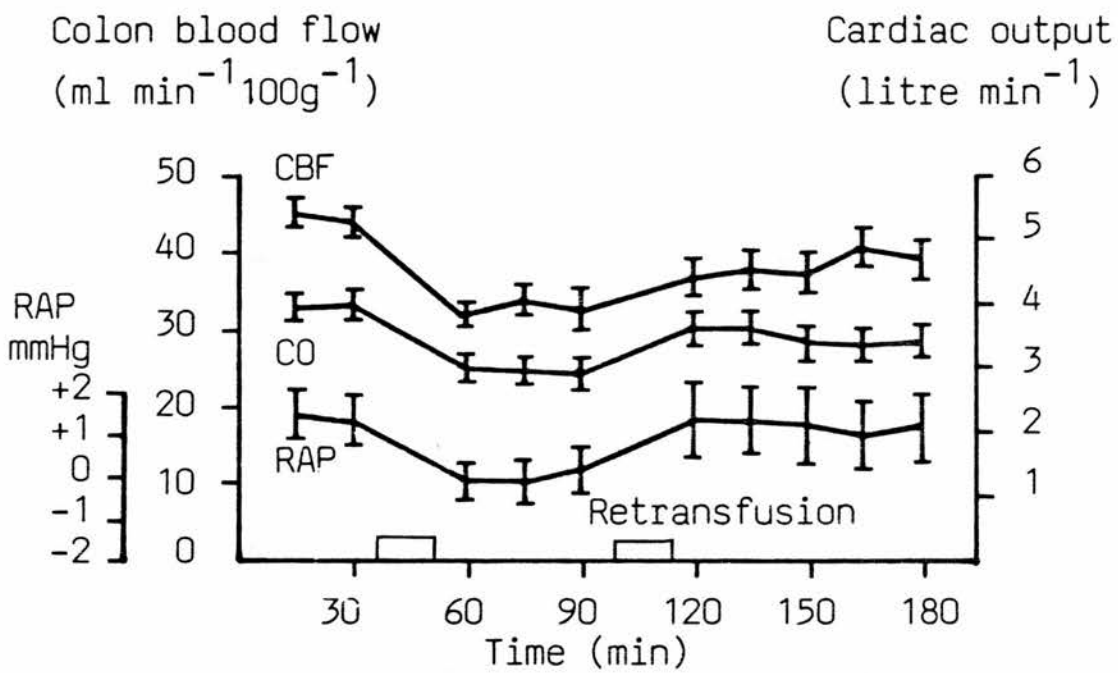
Colonic blood flow decreased by 27.4% from 44.1 ± 1.9 ml min^{-1} 100 g^{-1} (mean ± sem) to 32.0 ± 1.2 ml min^{-1} 100 g^{-1} ($p < 0.0005$). Colonic oxygen availability decreased by a similar proportion (Figure 6.3). Colon vascular resistance increased by 35.4% from 3.47 ± 0.20 unit to 4.70 ± 0.20 unit ($p < 0.001$). Colonic oxygen consumption did not change significantly.

[**6.3.2**] Effects of retransfusion

The mean values of arterial pressure and heart rate during the experiment are shown in Figure 6.4. Arterial pressure remained unchanged throughout the period of hypovolaemia, and after retransfusion. Heart rate increased during hypovolaemia, but returned to pre-haemorrhage values after transfusion. In Figure 6.5, the values of colonic blood flow, cardiac output and right atrial pressure have been plotted at each measurement point throughout the experiment. Data from Figures 6.4 and 6.5, together with the derived values of colonic vascular resistance and colonic oxygen consumption, are detailed in Tables 6.1 and 6.2. The decreases in cardiac output and right atrial pressure following haemorrhage were immediate and sustained, as was the fall in colonic blood flow. However, following retransfusion, central venous pressure returned to its pre-haemorrhage value, while both cardiac output and colonic blood flow remained significantly ($p < .025$) below their respective pre-haemorrhage values throughout the 60 min period after retransfusion. Retransfusion did not reverse the colonic vasoconstriction produced by haemorrhage, and colonic vascular resistance remained significantly ($p < 0.01$) higher than the pre-haemorrhage values throughout the post-transfusion period. There were no significant changes in colonic



Changes in heart rate (upper values) and mean arterial pressure (MAP) before and after haemorrhage and retransfusion. Mean values are plotted. Bars represent sem. Haemorrhage of 15% of blood volume over a 20 min period was started at 35 min. Retransfusion over a 20 min period was started at 95 min. Values shown in Table 6.2. No significant changes in arterial pressure.



Changes in colonic blood flow (CBF), cardiac output (CO) and right atrial pressure (RAP) before and after haemorrhage and retransfusion. Mean values are plotted. Bars represent sem. Haemorrhage of 15% of blood volume over a 20 min period was started at 35 min. Retransfusion over a 20 min period was started at 95 min. Values shown in Tables 6.1 and 6.2. Significance values discussed in text.

TABLE 6.1 Effect of 15% haemorrhage followed by retransfusion on colonic blood flow, vascular resistance and oxygen consumption in nine dogs. Values represent mean (sem).

Time	Colonic blood flow (ml min^{-1} 100 g^{-1})	Colonic vascular resistance (unit)	Colonic oxygen consumption (ml min^{-1} 100 g^{-1})
15 min	44.9 (1.8)	3.43 (0.19)	1.14 (0.08)
30 min	44.1 (1.9)	3.47 (0.20)	1.10 (0.10)
Haemorrhage	**$p < 0.0005$**	**$p < 0.001$**	**n.s.**
60 min	32.0 (1.2)	4.70 (0.20)	1.04 (0.13)
75 min	33.8 (1.9)	4.55 (0.30)	1.13 (0.11)
90 min	32.6 (2.8)	4.92 (0.50)	1.00 (0.15)
Retransfusion	**$p < 0.02$**	**n.s.**	**n.s.**
120 min	36.9 (2.5)	4.21 (0.28)	1.15 (0.09)
135 min	37.9 (2.5)	4.05 (0.26)	1.14 (0.12)
150 min	37.4 (2.5)	4.05 (0.29)	1.03 (0.07)
165 min	40.7 (2.6)	3.85 (0.23)	1.21 (0.12)
180 min	39.3 (2.4)	3.97 (0.23)	1.15 (0.11)

TABLE 6.2 Effect of 15% haemorrhage followed by retransfusion on systemic parameters in nine dogs. Values represent mean (sem).

Time	Cardiac output (litre min^{-1})	Heart rate (beat min^{-1})	Mean arterial pressure (mm Hg)	Right atrial pressure (mm Hg)
15 min	3.96 (0.18)	170.6 (8.8)	151.9 (4.8)	+ 1.2 (0.5)
30 min	4.00 (0.21)	171.7 (9.2)	150.4 (4.6)	+ 1.1 (0.5)
Haemorrhage	**$p < 0.0005$**	**$p < 0.002$**	**n.s.**	**$p < 0.002$**
60 min	2.98 (0.21)	184.4 (9.3)	148.8 (4.0)	- 0.2 (0.4)
75 min	2.94 (0.20)	185.0 (9.2)	149.6 (3.8)	- 0.3 (0.5)
90 min	2.91 (0.20)	188.3 (9.6)	149.4 (3.7)	0.0 (0.5)
Retransfusion	**$p < 0.002$**	**$p < 0.002$**	**n.s.**	**$p < 0.02$**
120 min	3.63 (0.25)	176.1 (7.5)	150.2 (3.4)	+ 1.1 (0.8)
135 min	3.63 (0.27)	175.6 (7.1)	148.8 (3.5)	+ 1.1 (0.7)
150 min	3.40 (0.24)	172.2 (7.1)	146.7 (4.3)	+ 1.0 (0.8)
165 min	3.36 (0.25)	177.2 (7.1)	152.1 (3.3)	+ 0.8 (0.7)
180 min	3.39 (0.26)	174.4 (7.6)	152.0 (2.9)	+ 0.9 (0.7)

oxygen consumption at any time during the experiment. Base excess and pH remained unaltered.

[6.4] DISCUSSION

Immediately after acute haemorrhage, there is a reduction in the circulating blood volume, and a consequent reduction of cardiac filling pressures. This causes a reduction of cardiac output and, usually, of arterial pressure. These reductions of pressure and flow cause compensatory responses in the cardiovascular system intended to restore arterial pressure and cardiac output to normal. Stimulation of baroreceptors and chemoreceptors results in an increase of sympathetic tone to the veins, the heart and the systemic resistance vessels, and a decrease of vagal tone to the heart (Kelman, 1977). In addition, there is increased stimulation of the adrenal medulla and enhanced secretion of adrenaline and noradrenaline. Increased sympathetic tone to resistance vessels causes vasoconstriction and an increase in total peripheral resistance, resulting in maintenance of arterial pressure despite a marked reduction in cardiac output. Vasoconstriction in vital organs such as the brain and heart is minimal (Green and Kepchar, 1959), and is maximal in tissues which are less essential for immediate survival, e.g. skin, kidneys and the splanchnic organs. The reduction in blood flow to these organs results in increased oxygen extraction and may lead to anaerobic metabolism and eventually hypoxic damage.

Severe haemorrhage is known to have adverse effects on the gut in several species including the dog (Chiu et al., 1970), the cat (Haglund, 1973) and man (Haglund et al., 1975), resulting in ischaemic or hypoxic lesions in the mucosa. In addition, the effects

of hypoperfusion on the bowel in shock states may have systemic cardiovascular effects (Lillihei, 1957; Lundgren and Haglund, 1978), depressing myocardial contractility and cardiac output still further.

Whitaker, Dixon and Greatorex (1970) and Vatner (1974) demonstrated that caudal mesenteric artery flow in dogs decreased significantly in response to moderate haemorrhage amounting to 10-15% of blood volume, and that retransfusion did not restore blood flow to normal. The results presented here show that colonic blood flow is also affected very significantly by moderate reductions in blood volume, suggesting that this structure, in common with the other intra-abdominal viscera, is subject to a reduction in perfusion in order to maintain arterial pressure and a normal flow to more vital organs. Although autoregulation in the colon is relatively poor, both metabolic and myogenic mechanisms (Chapter Two) would predict that vasodilatation would occur in response to minor reductions in perfusion pressure while mean arterial pressure was within the normal range (Kvietys and Granger, 1982). The observed increase in colonic vascular resistance must therefore be assumed to be the result of an increase in sympathetic vasoconstrictor activity, either mediated centrally through the sympathetic nerves or as a result of increased blood concentrations of catecholamines.

The failure of cardiac output to return to control values after retransfusion in spite of the restoration of right atrial pressure to the pre-haemorrhage value raises the possibility of the presence in the circulation of cardiodepressant substances, possibly released from the colon itself, despite the relatively minor degree of haemorrhage. Such substances have been demonstrated in many forms of shock (Lillihei, 1957; Lundgren and Haglund, 1978; Fisher et al.,

1973), and in the presence of splanchnic vasoconstriction produced by pharmacological means (Lefer et al., 1971). The restoration of arterial pressure was presumably achieved by a residual excess of sympathetic activity, and this was probably also responsible for the failure of colonic vascular resistance and colonic blood flow to return to their pre-haemorrhage values.

The decrease in oxygen availability to the colon as a result of mild hypovolaemia did not result in a significant fall in oxygen consumption in the present study. However, following colonic anastomosis, when tissues are rendered relatively ischaemic by surgical trauma and division of mesentery, such a decrease in oxygen availability might be more critical. Schrock , Deveney and Dunphy (1973) noted an increase in anastomotic breakdown rate from 4.4% in patients who remained normotensive to 10.7% in hypotensive patients in whom the cause of the reduced arterial pressure was probably hypovolaemia, and from 3.3% in patients who required no blood transfusion in the 24 hr period following the start of colonic surgery to 8.4% and 16.2% in patients requiring 2 - 3 and more than four units of blood respectively.

In any event, the present investigations suggest that even mild degrees of hypovolaemia have adverse effects on colonic haemodynamics, and should be avoided. In addition, there appears to be evidence to suggest that clinical monitoring of parameters other than arterial pressure and heart rate alone should be considered seriously as a guide to adequate fluid replacement in patients undergoing colonic surgery.

CHAPTER SEVEN

THE EFFECTS OF SPINAL NERVE BLOCK

[7.1] INTRODUCTION

Spinal nerve block with local anaesthetic solutions is known to result in vasodilatation in the portion of the body undergoing sympathetic blockade (Green et al., 1944). Blood flow to these areas is likely to reflect the balance between the degrees of vasodilatation and reduction of systemic arterial pressure. The clinical study presented in Chapter Three suggested that spinal nerve block, whether produced by the subarachnoid or extradural route, might contribute to a reduction in breakdown rate following colonic anastomosis. While a number of factors could contribute to such a reduction, an increase in blood flow to the colon might be anticipated, and could have beneficial effects on oxygen delivery to an anastomotic site. It was therefore felt appropriate to study the effects of spinal nerve block in the animal model.

[7.2] METHODS

[7.2.1] Technique of spinal nerve block

Thirty-five greyhounds, of weight ranging from 19 to 35 kg, were studied in these experiments. After laparotomy and insertion of monitoring lines, a period of 60 min was allowed for stabilisation of the preparation. A 20 gauge needle (Medicut™) was introduced at the interspace of the 6th and 7th lumbar vertebrae or the lumbosacral junction (L7 - S1), and advanced under radiographic control through the interlaminar space. It was found that the dura mater in the

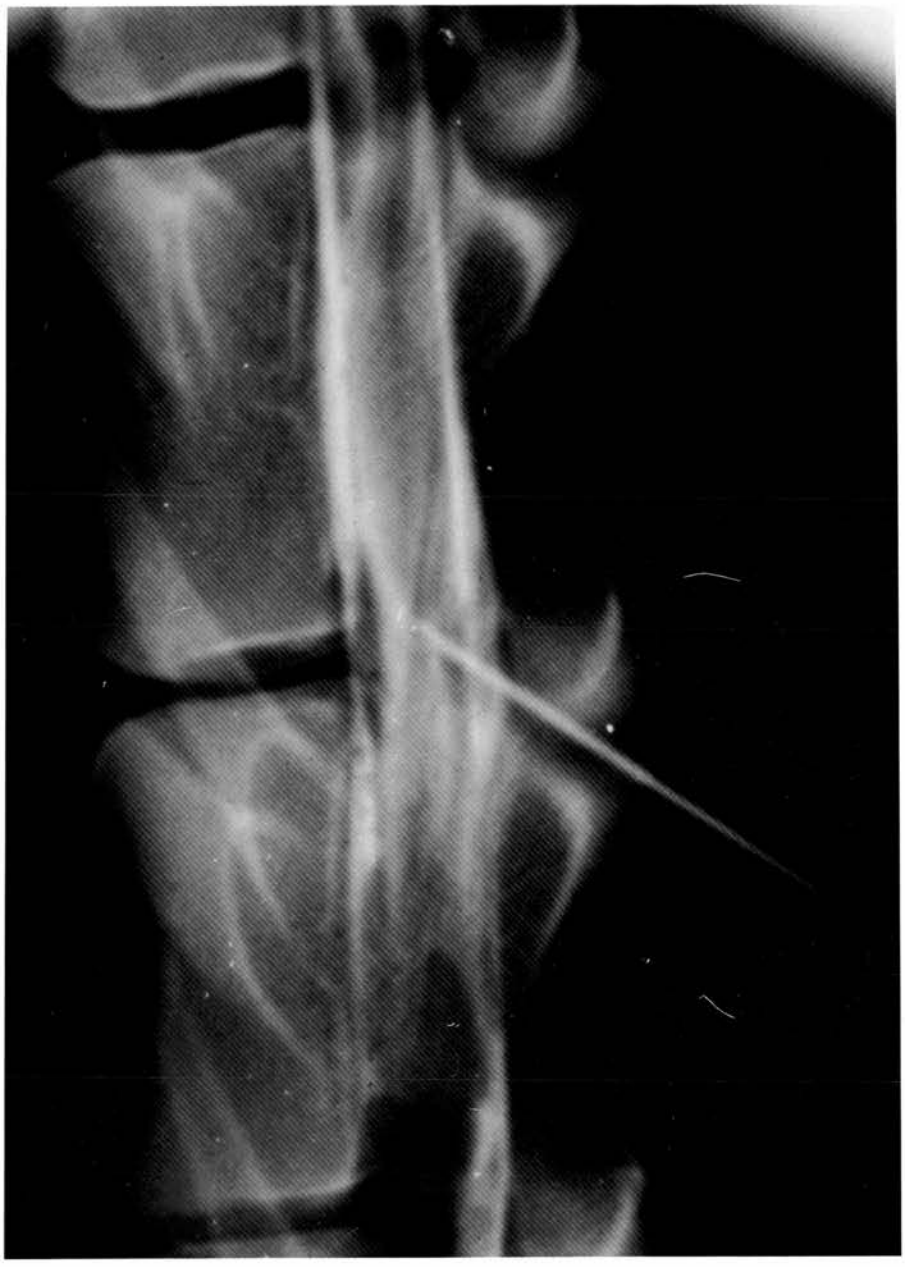
greyhound was extremely lax, and the cerebrospinal fluid pressure very low. Once the tip of the needle was in the spinal canal, it was therefore very difficult to identify whether the needle had entered the subarachnoid space. Accordingly, when the tip of the needle had passed through the interlaminar space, a small volume (0.5 - 1.5 ml) of meglumine iothalamate 60% (Conray 280™) was injected to outline the extradural space. On advancing the needle, indentation of the dura could be seen clearly (Figure 7.1) until dural puncture occurred. When the tip of the needle lay in the subarachnoid space, bupivacaine 0.5% was injected at a dose of 0.2 ml kg^{-1} to induce spinal nerve block. In one animal, meglumine iothalamate was injected into the subarachnoid space to demonstrate that fluids introduced into the cerebrospinal fluid behaved in the predicted manner (Figure 7.2).

In 23 animals, all cardiovascular parameters were measured and blood gas analysis performed immediately before, and 20 min after completion of, the spinal nerve block.

[**7.2.2**] Hypocapnia and hypercapnia

In 12 animals, the effects of changes in arterial P_{CO_2} were studied before and after institution of the block. After stabilisation, measurements were performed at 15 min intervals throughout the experiment. After two control groups of measurements, acute hypocapnia to an arterial P_{CO_2} between 2.1 and 3.1 kPa was induced by doubling the inspired tidal volume, and the measurements were repeated. Arterial P_{CO_2} was then restored to normal, and two further groups of measurements made. Acute hypercapnia was induced by the addition of carbon dioxide to the inspired gas mixture to produce an

Lateral radiograph of the lumbar spine of a dog after injection of radio-opaque dye into the extradural space to identify the dura mater. A needle has been introduced into the extradural space through the interlaminar space. Radio-opaque dye has travelled towards the head (upwards in picture) and caudally. The posterior extradural space is outlined clearly and is being indented by the tip of the needle. The white line running from top to bottom to the left of the picture is a portion of the mesenteric arterial catheter lying in the aorta.



Lateral radiograph of the lumbar spine of a dog after injection of radio-opaque dye into the cerebrospinal fluid (CSF) to outline the subarachnoid space. A needle has been introduced through the interlaminar space, and has pierced the dura posteriorly. Dye has mixed with CSF and can be seen faintly outlining the subarachnoid space towards the head (top). There is also some undiluted dye in the extradural space both anteriorly and posteriorly.

arterial P_{CO_2} between 10.0 and 12.5 kPa, and the measurements were repeated. Arterial P_{CO_2} was once again restored to normal, and two final sets of measurements performed. Subarachnoid spinal nerve block was then performed, and, after 20 min, all measurements and P_{CO_2} changes undertaken before spinal nerve block were repeated.

[7.2.3] Hypovolaemia

In five dogs, the effects of moderate hypovolaemia after stabilisation under spinal nerve block were studied. An estimated 15% of blood volume was removed at a steady rate over a 20 min period (see Chapter Six), measurements being recorded 5 min before and 5 min after the period of haemorrhage.

[7.2.4] Intravenous methoxamine

In three dogs, the direct alpha-receptor agonist methoxamine was administered intravenously after the effects of spinal nerve block had been measured. The dose administered was titrated against mean arterial pressure, the aim being to restore arterial pressure to the value observed prior to institution of the block. The mean dose of methoxamine required was 4 mg. All measurements were repeated 10 min after the injection of methoxamine had been completed.

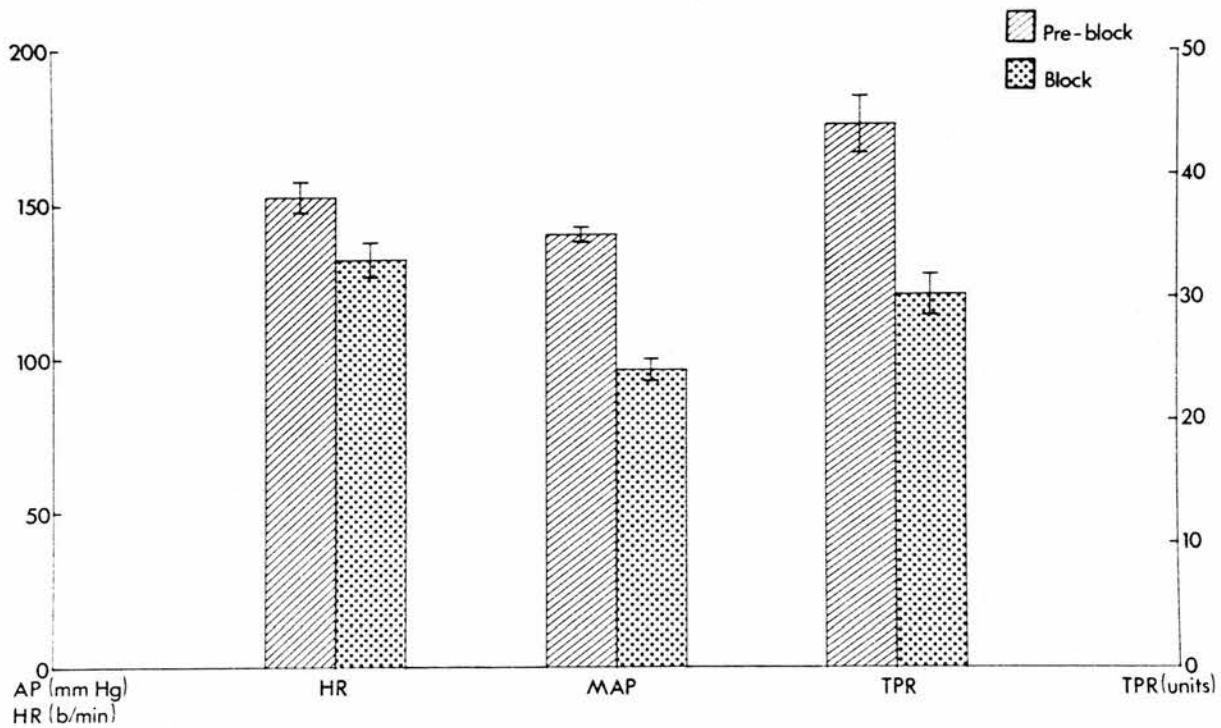
[7.3] RESULTS

[7.3.1] Effects of spinal nerve block (Table 7.1).

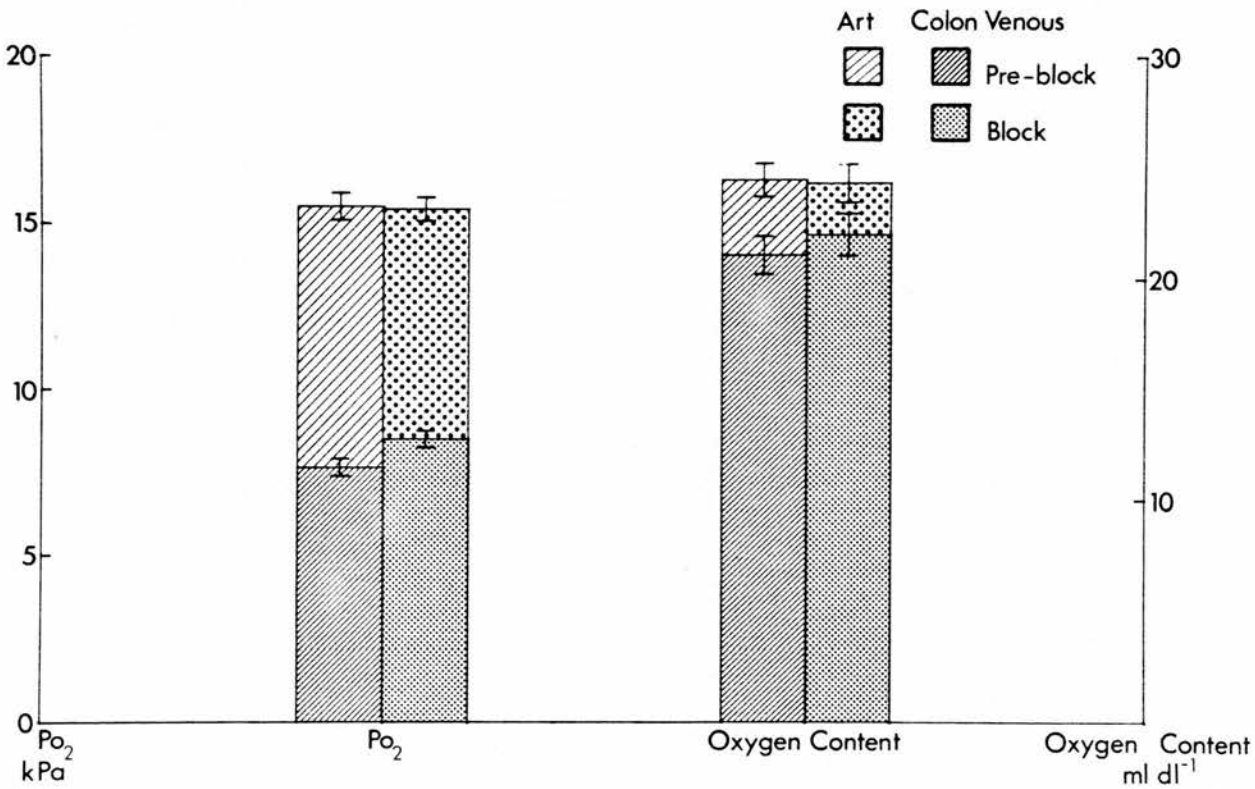
Subarachnoid spinal nerve block produced a decrease in mean arterial pressure of 31.1% and in heart rate of 12.2% (Figure 7.3). Total peripheral resistance decreased by 31.4%. Cardiac output did not alter significantly. Colonic blood flow increased by 22.3%, and

TABLE 7.1 Effects of spinal nerve block. Values from 35 dogs expressed as mean (sem).

	Before block	p	Block
Heart rate (beat min^{-1})	151.3 (4.8)	< 0.0001	132.8 (5.4)
Mean systemic arterial pressure (mm Hg)	140.0 (2.2)	< 0.0001	96.5 (3.4)
Mean pulmonary arterial pressure (mm Hg)	12.8 (0.7)	< 0.001	11.4 (0.6)
Right atrial pressure (mm Hg)	0.84 (0.15)	n.s.	0.90 (0.21)
Cardiac output (litre min^{-1})	3.38 (0.16)	n.s.	3.29 (0.15)
Total peripheral resistance (unit)	44.2 (2.3)	< 0.0001	30.3 (1.7)
Arterial oxygen tension (kPa)	15.6 (0.4)	n.s.	15.5 (0.4)
Arterial oxygen content (ml dl^{-1})	24.55 (0.75)	n.s.	24.39 (0.86)
Mixed venous oxygen content (ml dl^{-1})	18.70 (0.46)	n.s.	18.79 (0.58)
Total oxygen consumption (ml min^{-1})	190.7 (10.8)	n.s.	177.1 (8.3)
Colon blood flow (ml min^{-1} 100 g^{-1})	36.7 (1.0)	< 0.001	44.9 (1.6)
Colon vascular resistance (unit)	3.92 (0.13)	< 0.0001	2.20 (0.09)
Colon venous oxygen tension (kPa)	7.7 (0.2)	< 0.001	8.5 (0.3)
Colon venous oxygen content (ml dl^{-1})	21.15 (0.86)	< 0.01	22.07 (0.95)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.33 (0.09)	< 0.01	1.10 (0.08)



Effects of spinal nerve block on heart rate (HR), mean arterial pressure (MAP) and total peripheral resistance (TPR). Values are from 35 dogs. Blocks represent mean values before (cross-hatched) and during (stippled) spinal nerve block. Bars represent sem. Significance values shown in Table 7.1.



Effects of spinal nerve block on arterial (coarse shading) and colonic venous (fine shading) oxygen tension and oxygen content. Values are from 35 dogs. Blocks represent mean values before (cross-hatched) and during (stippled) spinal nerve block. Bars represent sem.

there was a decrease of 43.9% in colonic vascular resistance. There was a significant decrease in the difference between oxygen tensions in arterial and colonic venous blood after the block, and this was reflected in the oxygen content differences (Figure 7.4). Spinal nerve block was associated with a significant decrease in colonic oxygen consumption.

[7.3.2] Effects of hypocapnia (Tables 7.2 and 7.3).

The values of P_aCO_2 at normocapnia and hypocapnia were 5.40 ± 0.12 kPa (mean ± sem) and 2.55 ± 0.11 kPa before spinal nerve block, and 5.21 ± 0.13 kPa and 2.51 ± 0.08 kPa during the block. Hypocapnia produced a small but statistically significant decrease in arterial pressure both before and after spinal nerve block, and small but significant increases in heart rate.

Colonic blood flow was reduced by 19.3% in response to hypocapnia before the block, and by 30.0% after the block (Figure 7.5), and there were increases of 16.4% and 32.9% in colonic vascular resistance before and after the block respectively.

There were no significant changes in total peripheral resistance or total oxygen consumption in response to hypocapnia, irrespective of spinal nerve block. Hypocapnia produced no significant changes in colonic oxygen consumption, or in arterial-venous oxygen tension or oxygen content differences within the colon.

[7.3.3] Effects of hypercapnia (Tables 7.4 and 7.5).

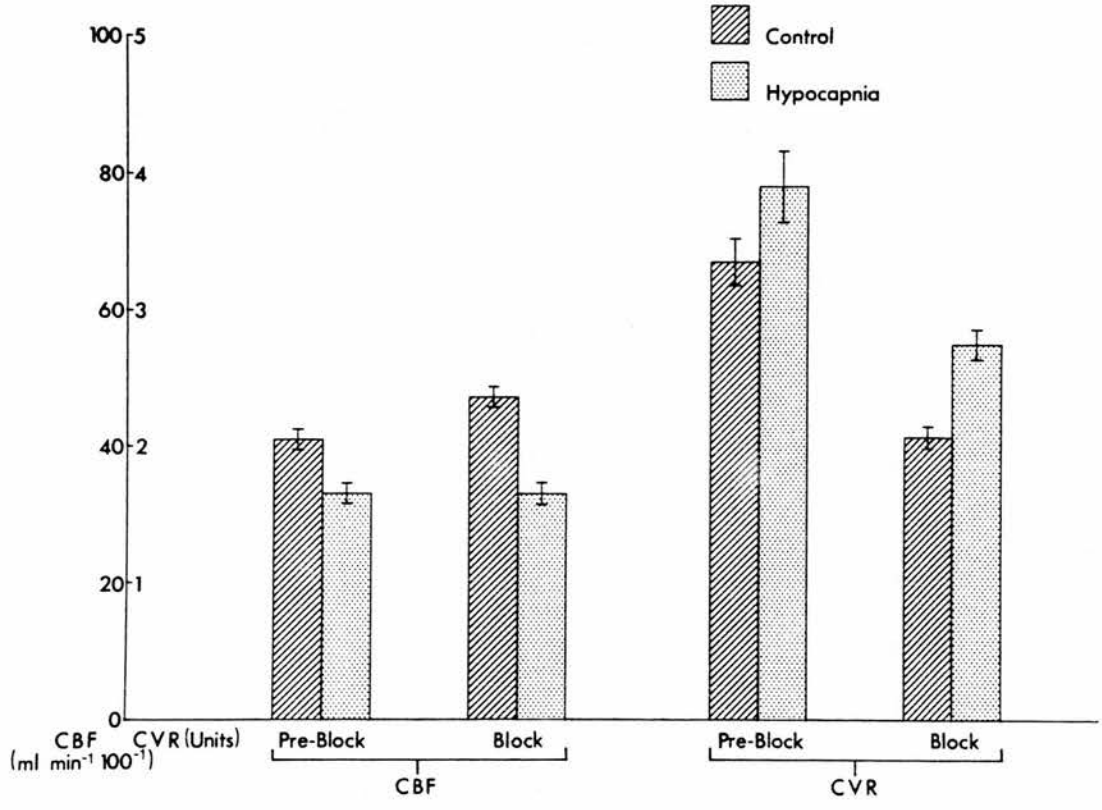
Arterial P_{CO_2} values during normocapnia and hypercapnia were 5.11 ± 0.12 kPa and 11.53 ± 0.77 kPa before institution of spinal nerve blockade, and 5.25 ± 0.17 kPa and 11.92 ± 0.56 kPa during the

TABLE 7.2 Effects of hypocapnia and spinal nerve block on systemic haemodynamics and oxygen consumption. Values from 12 dogs expressed as mean (sem).

	Before block			Block		
	Control	p	Hypocapnia	Control	p	Hypocapnia
Heart rate (beat min^{-1})	141.5 (6.3)	<0.001	151.0 (5.3)	104.0 (5.2)	<0.001	114.5 (5.1)
Mean arterial pressure (mm Hg)	135.8 (4.3)	<0.005	126.0 (5.5)	97.3 (4.1)	<0.01	90.2 (4.3)
Cardiac output (litre min^{-1})	4.84(0.35)	n.s.	5.05(0.38)	3.99(0.28)	n.s.	4.10(0.25)
Total peripheral resistance (unit)	32.4 (3.6)	n.s.	29.5 (3.4)	28.0 (2.6)	n.s.	25.1 (2.8)
Total oxygen consumption (ml min^{-1})	230.1 (17.1)	n.s.	218.3 (21.8)	214.4 (10.1)	n.s.	217.8 (15.0)

TABLE 7.3 Effects of hypocapnia and spinal nerve block on colonic haemodynamics and oxygen consumption. Values from 12 dogs expressed as mean (sem).

	Before block			Block		
	Control	p	Hypocapnia	Control	p	Hypocapnia
Colon blood flow (ml min^{-1} 100 g^{-1})	41.0 (1.5)	<0.0005	33.1 (1.5)	47.3 (1.5)	<0.0001	33.1 (1.6)
Colon vascular resistance (unit)	3.36(0.17)	<0.005	3.91(0.26)	2.07(0.08)	<0.0005	2.75(0.11)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.20(0.20)	n.s	1.41(0.25)	1.06(0.12)	n.s.	1.17(0.11)



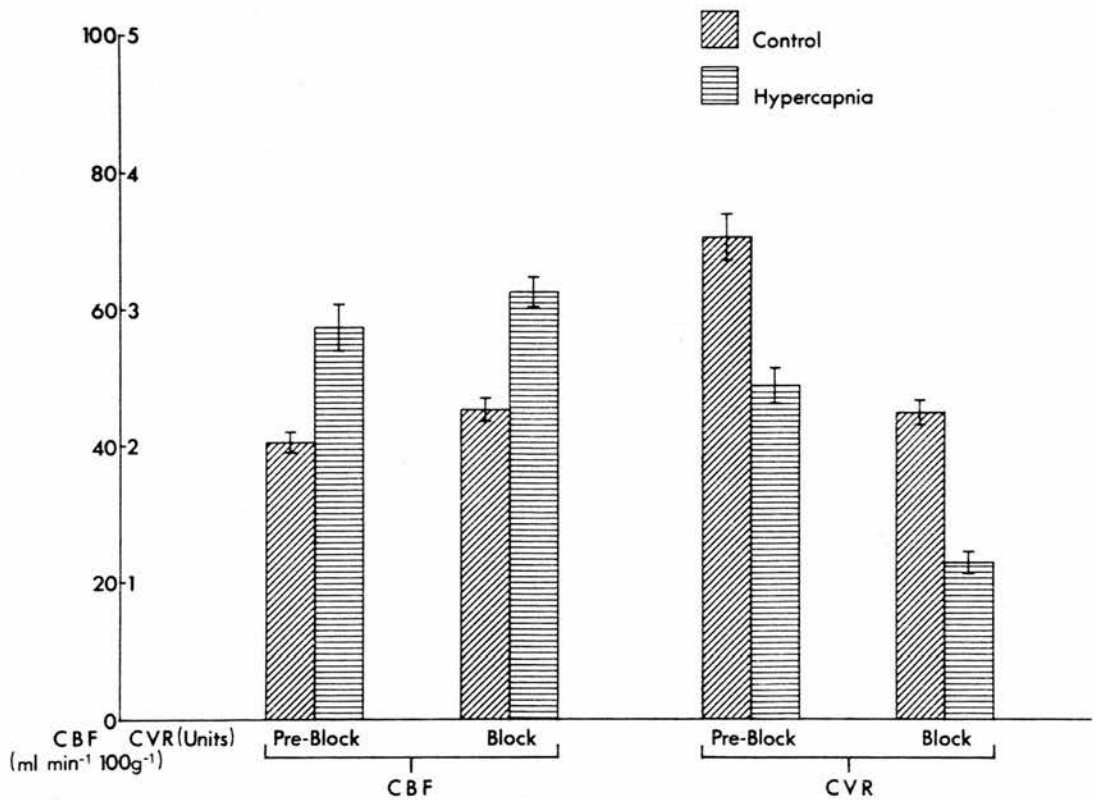
Changes in colonic blood flow (CBF) and colonic vascular resistance (CVR) resulting from hypocapnia before and during spinal nerve block. Values are from 12 dogs. Blocks represent mean values at normal P_aCO_2 (cross-hatched) and during hypocapnia (stippled). Bars represent sem. Significance values shown in Table 7.3.

TABLE 7.4 Effects of hypercapnia and spinal nerve block on systemic haemodynamics and oxygen consumption. Values from 12 dogs expressed as mean (sem).

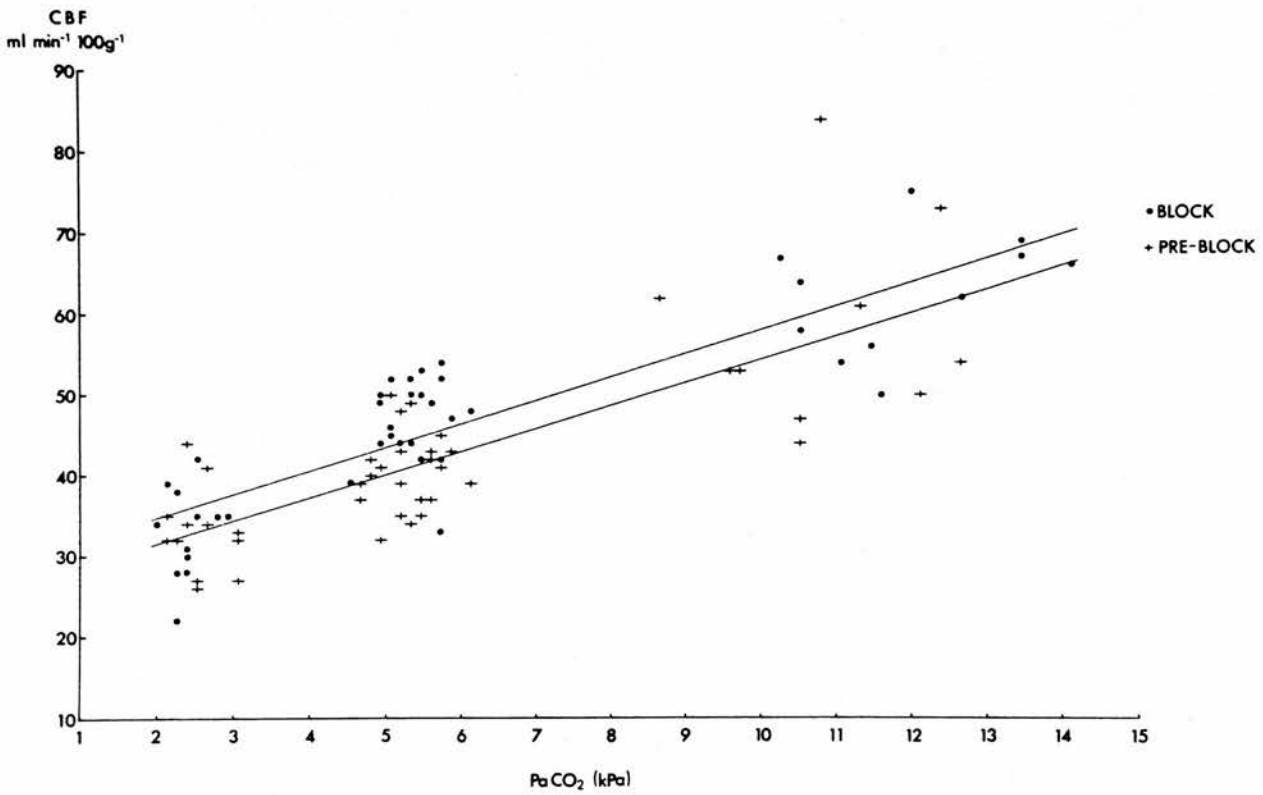
	Before block			Block		
	Control	p	Hypercapnia	Control	p	Hypercapnia
Heart rate (beat min^{-1})	134.5 (7.7)	n.s.	133.5 (4.4)	98.9 (8.4)	n.s.	106.9 (6.8)
Mean arterial pressure (mm Hg)	140.8 (4.0)	n.s.	135.8 (4.9)	101.5 (5.3)	< 0.0001	70.2 (4.3)
Cardiac output (litre min^{-1})	4.30(0.25)	<0.05	5.30(0.41)	4.08(0.32)	n.s.	4.34(0.30)
Total peripheral resistance (unit)	34.8 (2.3)	n.s.	28.8 (2.5)	28.0 (2.0)	< 0.0005	17.6 (1.7)
Total oxygen consumption (ml min^{-1})	231.3 (22.3)	n.s.	238.7 (53.9)	204.0 (9.2)	n.s.	209.3 (31.6)

TABLE 7.5 Effects of hypercapnia and spinal nerve block on colonic haemodynamics and oxygen consumption. Values from 12 dogs expressed as mean (sem).

	Before block			Block		
	Control	p	Hypercapnia	Control	p	Hypercapnia
Colon blood flow (ml min^{-1} 100 g^{-1})	40.5 (1.5)	<0.0005	57.4 (3.4)	45.3 (1.7)	<0.0001	62.6 (2.2)
Colon vascular resistance (unit)	3.53(0.17)	<0.0001	2.44(0.13)	2.24(0.09)	<0.0001	1.14(0.08)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.23(0.22)	n.s.	1.01(0.32)	1.11(0.47)	n.s.	1.18(0.27)



Changes in colonic blood flow (CBF) and colonic vascular resistance (CVR) resulting from hypercapnia before and during spinal nerve block. Values are from 12 dogs. Blocks represent mean values at normal P_aCO_2 (diagonal hatch) and during hypercapnia (horizontal hatch). Bars represent sem. Significance values in Table 7.5.

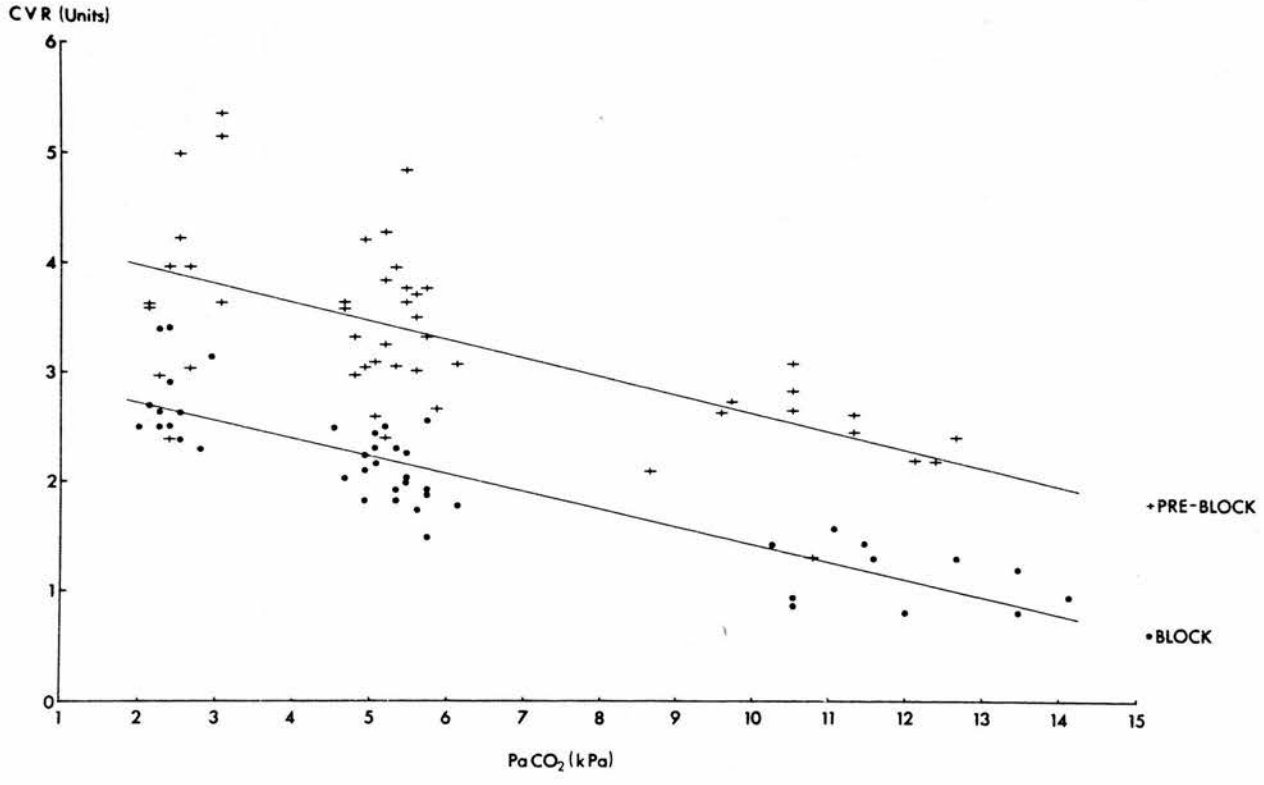


Relationships between colonic blood flow (CBF) and P_aCO_2 before (crosses) and during (circles) spinal nerve block. Values are from 12 dogs. The regression lines are represented by the equations:

Before block; $y = 2.86x + 25.82$ $r = 0.776$ $p < 0.001$

After block; $y = 3.13x + 28.21$ $r = 0.846$ $p < 0.001$

No significant difference between slopes; $t = 0.59$, d.f. = 91



Relationships between colonic vascular resistance (CVR) and P_aCO_2 before (crosses) and during (circles) spinal nerve block. Values are from 12 dogs. The regression lines are represented by the equations:

Before block; $y = -0.17x + 4.33$ $r = -0.628$ $p < 0.001$

After block; $y = -0.16x + 3.05$ $r = -0.874$ $p < 0.001$

No significant difference between slopes; $t = 0.25$, $d.f. = 91$

block. There were no significant alterations in arterial pressure or total peripheral resistance in response to hypercapnia before spinal nerve block, but after the block, increasing the P_aCO_2 resulted in a decrease of 30.8% in mean arterial pressure, and a decrease of 37.1% in total peripheral resistance. There were no significant changes in total oxygen consumption in response to an increased P_aCO_2.

Hypercapnia was associated with a 41.7% increase in colonic blood flow and a 30.9% decrease in colonic vascular resistance before spinal nerve block (Figure 7.6). The corresponding changes after the block had been performed were a 38.2% increase in colonic blood flow and a 49.1% decrease in colonic vascular resistance. Colonic oxygen consumption and arterial-venous oxygen tension and content differences were not altered significantly by hypercapnia before or during the block.

Figure 7.7 shows the relationship between colonic blood flow and arterial P_{CO_2} before and after spinal nerve block. There was a highly significant correlation coefficient for both regression lines, and it can be seen that, following the block, colonic blood flow was increased relative to the pre-block values throughout the range of arterial P_{CO_2}. In Figure 7.8, the relationship between colonic vascular resistance and arterial P_{CO_2} before and during the block is demonstrated. In both figures, there is no significant difference between the slopes of the regression lines before and after the block. The fact that the lines are more closely approximated in Figure 7.7 is, of course, the result of the decrease in arterial pressure in response to spinal nerve block.

[7.3.4] Effects of hypovolaemia

Haemorrhage of 15% of blood volume in the presence of spinal nerve block resulted in significant decreases in mean arterial pressure (26%), cardiac output (25%) and right atrial pressure (Table 7.6). There was no change in heart rate or in total peripheral resistance. Colonic blood flow decreased by 32%. There were small but statistically insignificant increases in colonic vascular resistance and colonic oxygen consumption.

[7.3.5] Effects of methoxamine

Table 7.7 shows the cardiovascular effects of methoxamine in three dogs. Because of the small number of animals studied, it is inappropriate to undertake statistical analysis of these data, and no firm conclusions can be drawn. However, after administration of a dose of intravenous methoxamine which restored arterial pressure to the level attained before institution of spinal nerve block, heart rate and cardiac output decreased. Colonic blood flow decreased in all animals to a value lower than that measured before the block. Colonic vascular resistance increased on average by 161% after methoxamine, compared with a mean increase of 62% in total peripheral resistance. Colonic oxygen consumption increased by 47%.

[7.4] DISCUSSION

[7.4.1] The effects of spinal nerve block

The technique used for spinal nerve block in these experiments was more intricate than that required for subarachnoid injection of local anaesthetic agents in the human. The canine interlaminar space is extremely narrow, and there is a lower pressure of cerebrospinal

TABLE 7.6 Effects of haemorrhage of 15% of blood volume during spinal nerve block. Values from five dogs expressed as mean (sem).

	Control	p	Hypovolaemia
Heart rate (beat min^{-1})	143.2 (6.1)	n.s.	132.8 (5.4)
Mean arterial pressure (mm Hg)	112.5 (2.7)	< 0.01	83.9 (2.2)
Right atrial pressure (mm Hg)	+ 1.10 (0.33)	< 0.001	- 0.10 (0.40)
Cardiac output (litre min^{-1})	3.18 (0.19)	< 0.01	2.40 (0.13)
Total peripheral resistance (unit)	35.2 (3.6)	n.s.	35.0 (2.9)
Colon blood flow (ml min^{-1} 100 g^{-1})	50.2 (4.2)	< 0.05	34.3 (5.4)
Colon vascular resistance (unit)	2.32 (0.24)	n.s.	2.80 (0.59)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	1.16 (0.11)	n.s.	1.37 (0.34)

TABLE 7.7 Effects of intravenous methoxamine administered during spinal nerve block to three dogs. Values represent mean (sem).

	Before block	Block	Methoxamine
Heart rate (beat min^{-1})	143.3 (8.8)	106.7 (6.7)	93.3 (14.8)
Mean arterial pressure (mm Hg)	148.3 (4.4)	103.3 (9.3)	146.7 (9.3)
Cardiac output (litre min^{-1})	3.7 (0.6)	3.2 (0.3)	2.4 (0.4)
Total peripheral resistance (unit)	43.1 (7.6)	33.3 (4.6)	54.0 (12.8)
Colonic blood flow (ml min^{-1} 100 g^{-1})	37.7 (3.2)	45.0 (3.1)	26.3 (5.0)
Colonic vascular resistance (unit)	4.0 (0.5)	2.3 (0.1)	5.9 (1.1)
Colonic oxygen consumption (ml min^{-1} 100 g^{-1})	1.1 (0.1)	0.8 (0.3)	1.2 (0.1)

fluid. A successful technique was described by Redderson, Uy and Anton (1974), although in some cases the needle had to be passed through bone. This was never necessary in the present experiments, and with radiological control the method described was not technically difficult and achieved consistent results. The possibility exists that the injection of radio-opaque dye into the extradural space might have had an effect on the spinal nerves. However, no effect was seen despite the intensive cardiovascular monitoring used.

Plain bupivacaine was selected as the local anaesthetic agent because it does not depend on gravity for its spread. The dogs were lying in a right lateral position on a non-tipping table, and it would have been difficult technically to obtain a bilateral high spinal block using a hyperbaric solution. Plain bupivacaine is slightly hypobaric with respect to cerebrospinal fluid at 37°C (densities 0.998 and 1.001 g cm^{-3} respectively), and spreads by volume displacement. The mean time to achieve maximum spread after lumbar injection of plain bupivacaine in the human is 19 min, and the duration of action in the thoracic region is approximately 2 hr (Chambers, Edstrom and Scott, 1981). In the present studies, no measurements were made until 20 min after subarachnoid injection had been completed, and the maximum duration of the experiments undertaken after the initial measurements was 105 min.

Subarachnoid spinal nerve block was associated with a decrease of 44% in colonic vascular resistance. Despite a considerable decrease in mean arterial pressure, this produced a highly significant increase in colonic blood flow. The decrease in systemic peripheral resistance was 31%, which is of a greater order than that found by Sancetta and others (1952) in humans undergoing high spinal nerve

block, with a sensory level above T4, although Pugh and Wyndham (1950) found decreases in total peripheral resistance of up to 35% in patients with a similar level of block. It was difficult in the present study to determine the exact level of spinal nerve block in the dogs; it was desirable for humane reasons alone that general anaesthesia should be continued throughout the experiment. However, the fact that bradycardia occurred suggests that the sympathetic cardiac fibres were being affected, and thus that the level of block was probably up to the mid-thoracic region, making it equivalent to a "high" spinal anaesthetic. The general anaesthetic agent used may have reduced reflex vasoconstriction in the upper part of the body, thus exaggerating the decrease in total peripheral resistance. Nevertheless, the decrease in colonic vascular resistance was considerably greater than that in total peripheral resistance. This is contrary to the findings of Mueller, Lynn and Sancetta (1952), who found no significant change in splanchnic vascular resistance during high spinal anaesthesia at a time when total peripheral resistance was decreased. It is possible that a degree of hypovolaemia in Mueller's study was responsible for the difference.

As the arterial oxygen tension and content remained unchanged before and after spinal nerve block, the 22% increase in colonic blood flow resulted in a similar percentage increase in oxygen availability. The colonic venous P_{O_2}, which probably reflects fairly accurately the colonic end-capillary P_{O_2}, was significantly increased, and it seems reasonable to suggest that the capillary - tissue P_{O_2} gradient would be correspondingly increased. The arterial - colonic venous oxygen content difference was substantially decreased, but despite the increase in colonic blood flow, colonic oxygen con-

sumption was decreased by an average of 17%. This may be the result of a decrease in metabolic activity following the removal by spinal nerve block of central sympathetic, and particularly parasympathetic, stimulation. (The parasympathetic nerve supply to the dog colon is from the sacral roots.)

[7.4.2] The effects of carbon dioxide changes

The effects on colonic blood flow and vascular resistance, and the effects on heart rate, mean arterial pressure and total peripheral resistance, of hypocapnia and hypercapnia before subarachnoid spinal nerve block in this study are comparable to those reported in Chapter Five. Although it was demonstrated in the work reported in that chapter that the effects of hypocapnia were due to the reduction in arterial P_{CO_2}, and not the physical effects of hyperventilation, such a demonstration was not undertaken following spinal nerve block. However, there were no changes in cardiac output or right atrial pressure during hypocapnia in the presence of spinal nerve block, and it seems unlikely that any important effect on colonic haemodynamics resulting from the increased tidal volume *per se* would have occurred without a change in one or both of these parameters.

Hypocapnia produced a slightly greater decrease in colonic blood flow after spinal nerve block, whereas hypercapnia following spinal block resulted in a large decrease in arterial pressure, which was reflected in a smaller percentage increase in colonic blood flow than that seen before the block, even though the absolute value was greater. Colonic vascular resistance was lower after spinal nerve block at each level of arterial P_{CO_2}.

A number of points of interest are raised by these findings.

1) Sympathetic nerve block did not produce maximal vasodilatation in the colonic vasculature, since an increase in arterial P_{CO_2} produced a further decrease in vascular resistance. This confirms earlier findings by Folkow (1949) and Pappenheimer (1952) in other areas of the body.

2) If, in the colon, changes in vascular resistance following alterations to arterial P_{CO_2} are a result of the direct effects of carbon dioxide on the vessels, partly countered by the opposing effects of the sympathetic nervous system, then it would be expected that the sympathetic denervation produced by spinal nerve block would result in larger alterations in vascular resistance in response to changes in P_{CO_2}, since the direct effects of carbon dioxide should be unopposed. Indeed, total peripheral resistance and mean arterial pressure decreased significantly in response to hypercapnia in the presence of spinal nerve block, but not before. However the degree of change in colonic vascular resistance in response to both hypocapnia and hypercapnia was similar before and after the block. It is possible that the concentrations of circulating catecholamines in the blood still change in response to alterations in arterial P_{CO_2}, although this must be a local effect of carbon dioxide on the adrenal medulla or sympathetic nerve endings, as the adrenal medulla is denervated by high spinal nerve block. However, it is unlikely that circulating catecholamine concentrations exert a major effect on the colonic vasculature, and it would seem reasonable to assume that the sympathetic compensation afforded to the colon against the effects of carbon dioxide is minimal.

[7.4.3] The effects of hypovolaemia

Spinal nerve block abolished the ability of the animals to maintain systemic arterial pressure following haemorrhage of 15% of blood volume, suggesting that this ability is mediated by an increase in sympathetic vasoconstrictor activity. Kennedy and others (1968) demonstrated a similar effect in man following haemorrhage of 10 ml kg^{-1}. The small increase in colonic vascular resistance in the present study contrasts with the highly significant increase which accompanied haemorrhage in the absence of spinal nerve block (Chapter Six). Despite the lack of a marked vasoconstrictor response to haemorrhage, colonic blood flow decreased by more than 30%, demonstrating that any benefit acquired from spinal nerve block in terms of improved colonic perfusion will be lost if hypovolaemia is permitted to occur.

[7.4.4] The effects of methoxamine

Methoxamine is a sympathomimetic agent with an entirely alpha effect, although it has been suggested that it may produce some blockade of ß-receptors (Karim, 1965). Its action at alpha receptors is mainly direct, although some indirect action has also been demonstrated. After intravenous injection, the drug acts within 2 min. Administration of methoxamine produces the systemic cardiovascular changes found in this study, namely an increase in arterial pressure, a decrease in cardiac output, and a reduction in heart rate. The last may be the result of vagal stimulation initiated by baroreceptors, or an effect of ß-receptor blockade. Methoxamine has been recommended for the treatment of hypotension induced by spinal nerve block (Vickers, Wood-Smith and Stewart, 1978). However, a comparison

between the changes in colonic and systemic haemodynamics found in this study suggest that the splanchnic circulation undergoes particularly severe vasoconstriction in response to methoxamine, as colonic vascular resistance increased by a far greater proportion than did total peripheral resistance. Colonic blood flow was reduced to values lower than those occurring before spinal nerve block.

[**7.4.5**] Clinical significance

If the findings of this study are applicable in man, it would appear that high spinal nerve block may provide the colon with an increased blood supply and oxygen availability. Patients anaesthetised using a nitrous oxide-oxygen-muscle relaxant technique tend to be artificially hyperventilated, resulting in arterial P_{CO_2} values of 3.5 - 4 kPa which will reduce colonic blood flow and oxygen availability. Most anaesthetists who use high spinal nerve block as an anaesthetic technique combine the block with a light general anaesthetic, and allow the patient to breathe spontaneously, partly as an aid in detection of the height of the block, but also because abdominal relaxation is so profound that muscle relaxants are unnecessary. Under these conditions, the patient's arterial P_{CO_2} has been shown to increase slightly to values of up to 7.2 kPa (Morgan and Norman, 1975). It would appear from the present study that this combination should produce a substantially increased colonic blood flow. In addition, spinal nerve block using an extradural catheter technique after operation would be expected to combine excellent analgesia with an improved blood flow to the anastomosis. Because of the relationship between blood flow and tissue healing, these techniques might contribute to a reduction in the frequency of anast-

omotic dehiscence. If the increase in blood flow to the colon is of benefit to patients undergoing colonic anastomosis, any advantage obtained from the use of spinal nerve block would be lost if hypotension were to be reversed using a pure alpha agonist such as methoxamine, or if hypovolaemia were to be permitted to occur.

CHAPTER EIGHT

THE EFFECTS OF HALOTHANE

[8.1] INTRODUCTION

Halothane is at present the most widely used of the modern volatile anaesthetic agents. During controlled ventilation at normocapnia, halothane is known to depress cardiac output by approximately 25% in healthy subjects at a concentration of just over 1 MAC[1], and by up to 50% at 2 MAC (Eger et al., 1970). Arterial pressure is reduced to a similar degree, while peripheral vascular resistance remains unchanged. Hepatic blood flow has been reported to decrease by 25 - 30% during the administration of halothane; splanchnic vascular resistance is said to remain unchanged (Epstein et al., 1966; Price et al., 1965). The hypercapnia which accompanies spontaneous ventilation using halothane results in an increase in cardiac output and arterial pressure, and a decrease in peripheral vascular resistance (Bahlman et al., 1972) relative to values at normocapnia. The combination of halothane and hypercapnia produces splanchnic vasodilatation, while IPPV increases splanchnic vascular resistance (Epstein et al., 1966). It could thus be inferred that halothane anaesthesia might reduce colonic blood flow, although alterations in arterial P_{CO_2} are likely to influence this effect. It was therefore appropri-

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[1]MAC of an inhaled anaesthetic agent is the minimum alveolar concentration which produces abolition of a motor response to surgical stimulation in 50% of individuals. MAC of halothane is 0.75% in man (Saidman et al., 1967) and 0.87% in the dog (Eger et al., 1965). Variations in MAC between species are partly due to differences in degree of the applied stimulus.

ate to study the effects of halothane and carbon dioxide on colonic blood flow using the dog model.

[8.2] METHODS

Eleven greyhounds, of weight ranging from 20 to 33 kg (mean 27.5), were studied in these experiments. After the standard preparation of the model, a 60 min period was allowed for stabilisation. During this period, and throughout the experiment, all cardiovascular measurements and blood gas analysis were undertaken at 15 min intervals. In addition, samples were obtained simultaneously on each occasion from the aortic, right atrial and colonic marginal vein catheters for the subsequent measurement of blood lactic acid and pyruvic acid concentrations using the methods described in section [5.2.6]. Following the recording of control measurements at normocapnia (arterial P_{CO_2} 5.1 - 5.6 kPa), hypocapnia to an arterial P_{CO_2} of 2.0 - 3.2 kPa was induced by hyperventilation in the manner described in previous chapters. Fifteen minutes later, measurements were repeated, and normocapnia restored. After two further sets of measurements, hypercapnia to arterial P_{CO_2} levels of 10.3 - 13.3 kPa was instituted by addition of carbon dioxide to the inspired gas mixture, and measurements repeated. The arterial P_{CO_2} was returned to normal, and a further set of measurements made.

Halothane was then added to the inspired gas mixture. Initially, 2% halothane was administered from a Fluotec Mk II vaporiser (Cyprane, Ltd.), and the concentration was then adjusted to produce a mean arterial pressure of approximately 100 mm Hg in order that results could be compared with those after spinal nerve block. In most animals, the final vaporiser setting was approximately 1%.

The actual inspired concentration was not measured. After a 30 min stabilisation period, a further set of measurements was undertaken. Then, hypocapnia and hypercapnia were again induced, and measurements repeated, as described above.

[8.3] RESULTS

[8.3.1] Effects of halothane

The administration of halothane reduced mean arterial pressure by an average of 32% from 149.5 ± 5.2 mm Hg (mean ± sem) to a mean value of 102.2 ± 6.2 mm Hg, close to the target of 100 mm Hg (Table 8.1). This decrease in arterial pressure was accompanied by reductions of 14% in mean heart rate, 20% in mean cardiac output, and 14% in mean total peripheral resistance. Mean colonic blood flow increased by 13%, and there was a 40% decrease in mean colonic vascular resistance (Table 8.2). There was a small decrease in total oxygen consumption. Although there were significant decreases in colonic venous oxygen tension and content, there was also a small decrease in arterial oxygenation, and colonic oxygen consumption was not altered significantly by the administration of halothane.

There were no significant changes in arterial or mixed venous concentrations of lactate and pyruvate, but there was a statistically significant increase in the colonic venous concentration of lactate during the administration of halothane. However, the lactate/pyruvate ratios from all three sites remained unchanged after the introduction of halothane. The arterial pyruvate concentration was significantly ($p < 0.05$) higher in arterial blood during halothane administration than in mixed venous or colonic venous blood, but there were no significant differences in the concentrations of lactate, or the

TABLE 8.1 Effects of halothane administration on systemic parameters. Values from 11 dogs expressed as mean (sem).

	Before halothane	p	Halothane
Heart rate (beat min^{-1})	144.5 (5.4)	< 0.0001	124.4 (5.1)
Mean systemic arterial pressure (mm Hg)	149.5 (5.2)	< 0.0001	102.2 (6.2)
Mean pulmonary arterial pressure (mm Hg)	12.3 (0.9)	n.s.	12.2 (0.7)
Right atrial pressure (mm Hg)	0.50 (0.29)	n.s.	1.36 (0.34)
Cardiac output (litre min^{-1})	4.95 (0.28)	< 0.0001	3.98 (0.27)
Total peripheral resistance (unit)	31.1 (1.9)	< 0.001	26.9 (2.4)
Arterial oxygen tension (kPa)	17.4 (0.6)	n.s.	16.5 (0.7)
Arterial oxygen content (ml dl^{-1})	25.54 (0.79)	n.s.	24.99 (0.62)
Mixed venous oxygen content (ml dl^{-1})	23.14 (0.64)	n.s.	23.30 (0.51)
Total oxygen consumption (ml min^{-1})	194.4 (11.1)	< 0.02	167.9 (11.0)
Arterial lactate concentration (µmol $litre^{-1}$)	737.1 (84.9)	n.s.	695.7 (87.8)
Arterial pyruvate concentration (µmol $litre^{-1}$)	71.3 (12.1)	n.s.	76.6 (8.6)
Arterial lactate/pyruvate ratio	11.87 (1.65)	n.s.	9.94 (1.19)
Mixed venous lactate concentration (µmol $litre^{-1}$)	678.6 (96.2)	n.s.	592.9 (89.4)
Mixed venous pyruvate concentration (µmol $litre^{-1}$)	69.7 (6.5)	n.s.	60.9 (7.3)
Mixed venous lactate/pyruvate ratio	9.70 (1.24)	n.s.	10.39 (1.90)

TABLE 8.2 Effects of halothane administration on colonic parameters. Values from 11 dogs expressed as mean (sem).

	Before halothane	p	Halothane
Colon blood flow (ml min^{-1} 100 g^{-1})	40.8 (2.7)	< 0.02	45.9 (2.5)
Colon vascular resistance (unit)	3.87 (0.38)	< 0.0001	2.31 (0.21)
Colon venous oxygen tension (kPa)	7.1 (0.2)	< 0.01	6.7 (0.2)
Colon venous oxygen content (ml dl^{-1})	21.46 (0.80)	< 0.05	20.53 (0.58)
Colon oxygen consumption (ml min^{-1} 100 g^{-1})	0.97 (0.16)	n.s.	0.73 (0.07)
Colon lactate concentration (µmol $litre^{-1}$)	592.5 (66.8)	< 0.01	716.3 (74.3)
Colon pyruvate concentration (µmol $litre^{-1}$)	55.9 (7.0)	n.s.	63.0 (8.9)
Colon lactate/pyruvate ratio	11.69 (2.16)	n.s.	12.48 (1.76)

lactate/pyruvate ratios, between samples from the three sites either before or during the administration of halothane.

[**8.3.2**] Comparison of halothane and spinal nerve block

The differences in haemodynamic changes between spinal nerve block (data from Chapter Seven) and the administration of halothane at a concentration resulting in a similar mean arterial pressure are summarised in Table 8.3. The changes shown in this table represent the mean of the percentage changes of each parameter, rather than the percentage change of the mean value. Thus, some values differ slightly from the percentage changes reported in section [8.3.1]. The only parameters to differ significantly between the two experiments were cardiac output and total peripheral resistance. A similar percentage reduction in arterial pressure was achieved almost entirely by a decrease in peripheral resistance in response to spinal nerve block, but by a combination of decreased cardiac output and reduced peripheral resistance when halothane was administered.

[**8.3.3**] Effects of hypocapnia (Tables 8.4 and 8.5)

Hypocapnia (P_aCO_2 2.52 $\pm$ 0.12 kPa) induced during halothane administration resulted in small but statistically significant decreases in mean arterial pressure, heart rate and total peripheral resistance, and a significant increase in cardiac output in comparison with the values at normocapnia (P_aCO_2 5.20 $\pm$ 0.07 kPa). The changes in these parameters were proportionately similar to those which occurred in response to a similar degree of hypocapnia (P_aCO_2 2.49 $\pm$ 0.12 kPa) before halothane administration (P_aCO_2 at normocapnia 5.21 $\pm$ 0.08 kPa). There was a reduction in colonic blood flow

TABLE 8.3 Comparison of mean (sem) percentage changes in measured parameters in response to the induction of spinal nerve block in 35 dogs and the administration of halothane in 11 dogs.

	Spinal nerve block	p	Halothane
Heart rate	- 11.9 (2.1)	n.s.	- 13.9 (1.8)
Mean systemic arterial pressure	- 30.5 (2.7)	n.s.	- 31.6 (3.2)
Mean pulmonary arterial pressure	- 8.9 (2.9)	n.s.	- 1.8 (5.0)
Cardiac output	- 1.4 (4.6)	< 0.005	- 23.4 (2.8)
Total peripheral resistance	- 30.3 (3.3)	< 0.01	- 13.1 (2.9)
Arterial oxygen content	- 0.7 (0.3)	n.s.	- 1.9 (0.2)
Mixed venous oxygen content	+ 0.5 (0.2)	n.s.	+ 0.7 (0.3)
Total oxygen consumption	- 3.8 (4.2)	n.s.	- 12.9 (4.9)
Colon blood flow	+ 22.7 (6.0)	n.s.	+ 12.4 (4.2)
Colon vascular resistance	- 44.3 (3.2)	n.s.	- 40.5 (2.9)
Colon venous oxygen content	+ 4.4 (9.8)	n.s.	- 4.3 (8.7)
Colon oxygen consumption	- 17.3 (4.0)	n.s.	- 24.5 (3.6)

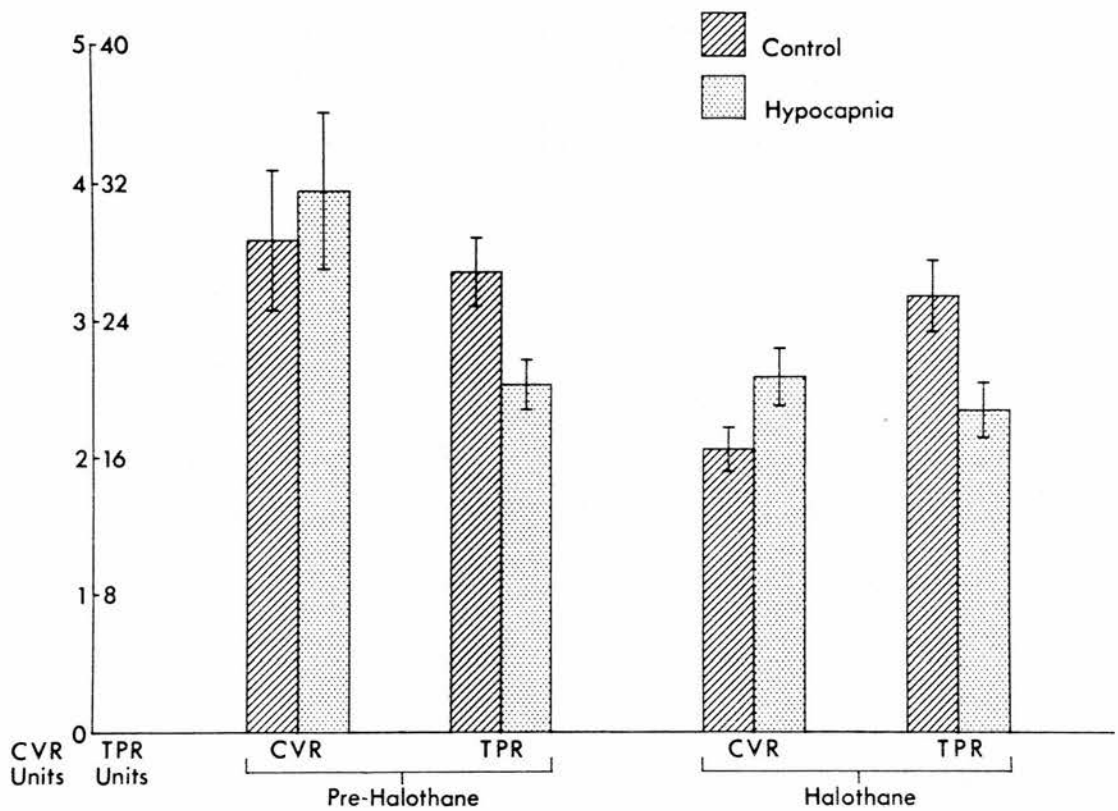
TABLE 8.4 Effects of hypocapnia on systemic haemodynamics and oxygen consumption before and during halothane administration. Values from 11 dogs expressed as mean (sem).

	Before halothane			Halothane		
	Control	p	Hypocapnia	Control	p	Hypocapnia
Heart rate (beat min^{-1})	150.5 (4.9)	n.s.	160.5 (5.9)	120.5 (5.2)	< 0.005	126.4 (4.7)
Mean arterial pressure (mm Hg)	140.5 (7.1)	< 0.005	114.9 (8.9)	99.5 (5.6)	< 0.005	85.5 (6.1)
Cardiac output (litre min^{-1})	5.15(0.36)	< 0.05	5.62(0.39)	3.94(0.24)	< 0.05	4.46(0.24)
Total peripheral resistance (unit)	28.2 (1.9)	< 0.001	20.9 (1.5)	26.1 (2.0)	< 0.001	19.7 (1.7)
Total oxygen consumption (ml min^{-1})	178.1 (13.3)	< 0.005	230.9 (19.4)	166.5 (12.9)	n.s.	179.0 (19.1)

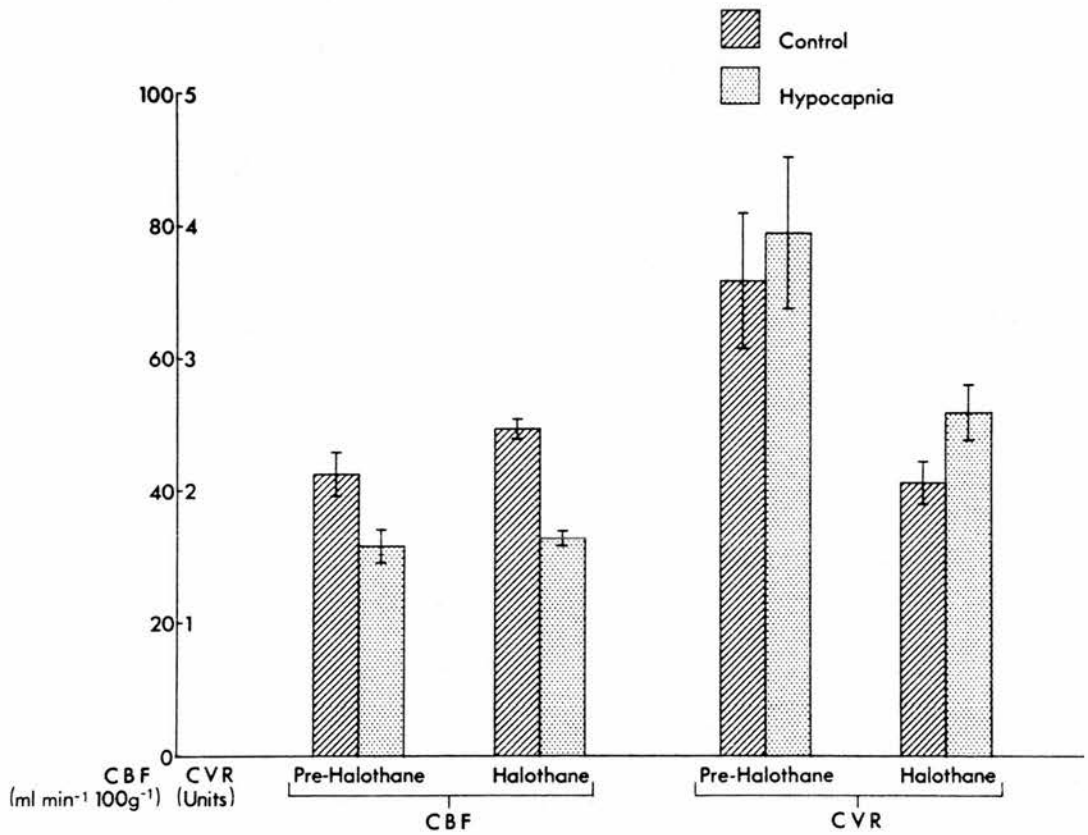
TABLE 8.5 Effects of hypocapnia on colonic haemodynamics and oxygen consumption before and during halothane administration. Values from 11 dogs expressed as mean (sem).

	Before halothane			Halothane		
	Control	p	Hypocapnia	Control	p	Hypocapnia
Colon blood flow ($ml\ min^{-1}\ 100\ g^{-1}$)	41.9 (3.0)	< 0.005	31.8 (2.3)	48.5 (1.6)	< 0.0001	33.0 (1.0)
Colon vascular resistance (unit)	3.64(0.45)	n.s.	3.91(0.52)	2.08(0.15)	< 0.001	2.61(0.19)
Colon oxygen consumption ($ml\ min^{-1}\ 100\ g^{-1}$)	1.04(0.15)	n.s.	1.17(0.21)	0.80(0.10)	n.s.	0.79(0.11)

TABLE 8.5



Changes in colonic vascular resistance (CVR) and total peripheral resistance (TPR) resulting from hypocapnia before and during administration of halothane. Values are from 11 dogs. Blocks represent mean values at normal P_aCO_2 (cross-hatched) and during hypocapnia (stippled). Bars represent sem. Significance values shown in Tables 8.4 and 8.5.



Changes in colonic blood flow (CBF) and colonic vascular resistance (CVR) resulting from hypocapnia before and during administration of halothane. Values are from 11 dogs. Blocks represent mean values at normal P_aCO_2 (cross-hatched) and during hypocapnia (stippled). Bars represent sem. Significance values shown in Table 8.5.

TABLE 8.6 Effects of hypocapnia on blood lactate and pyruvate concentrations during halothane administration. Values from 11 dogs expressed as mean (sem).

	Normocapnia	p	Hypocapnia
Arterial lactate concentration (μmol litre^{-1})	635.0 (89.4)	< 0.01	1155.0 (164.4)
Arterial pyruvate concentration (μmol litre^{-1})	60.0 (9.7)	< 0.02	82.4 (10.3)
Arterial lactate/pyruvate ratio	11.32 (1.43)	< 0.05	14.51 (1.98)
Mixed venous lactate concentration (μmol litre^{-1})	550.0 (92.3)	< 0.01	1197.1 (195.9)
Mixed venous pyruvate concentration (μmol litre^{-1})	50.4 (8.7)	< 0.02	80.4 (7.4)
Mixed venous lactate/pyruvate ratio	11.37 (1.06)	n.s.	14.70 (2.52)
Colon lactate concentration (μmol litre^{-1})	531.3 (75.7)	< 0.005	1117.5 (129.6)
Colon pyruvate concentration (μmol litre^{-1})	69.4 (10.8)	< 0.01	92.8 (14.6)
Colon lactate/pyruvate ratio	8.06 (0.95)	< 0.05	13.87 (2.58)

of 32%, and this was accompanied by an increase of 26% in colonic vascular resistance in response to hypocapnia during halothane administration. The corresponding changes before halothane administration were 24% and 7%. Colonic oxygen consumption remained unchanged when hypocapnia was induced, irrespective of halothane administration.

The differences between changes in total peripheral resistance and colonic vascular resistance in response to hypocapnia before and during halothane administration are shown in histogram form in Figure 8.1. It can be seen that despite the effect of halothane itself on the peripheral vascular tree, hypocapnia produced vasodilatation in the colonic vasculature but overall vasoconstriction both before and during halothane administration. The corresponding values of colonic blood flow are shown in Figure 8.2, together with the alterations in colonic vascular resistance in response to hypocapnia. It is clear that hypocapnia reduced colonic blood flow by a greater proportion during halothane administration than in the absence of halothane, despite the fact that colonic vascular resistance was substantially reduced by the administration of halothane.

During halothane administration, there were large and significant increases in lactate and pyruvate concentrations in arterial, mixed venous and colonic venous blood when hypocapnia was induced (Table 8.6). The lactate/pyruvate ratios increased, although the increase was not statistically significant in mixed venous blood. The colonic pyruvate concentration was significantly ($p < 0.05$) higher than that in mixed venous blood at normocapnia, but there were no significant differences in respect of lactate concentrations, or the lactate/pyruvate ratios, between arterial, mixed venous and colonic venous blood during normocapnia. There were no significant differ-

ences in lactate or pyruvate concentrations, or in lactate/pyruvate ratios, between blood samples from the three sites during hypocapnia. The corresponding data prior to the administration of halothane have been presented in Chapter Five (Table 5.5). Mixed venous and colonic venous lactate concentrations, and arterial and mixed venous pyruvate concentrations were significantly ($p < 0.05$) lower at normocapnia during halothane administration. There were no significant differences in any of these parameters during hypocapnia when data before and during halothane administration were compared.

[8.3.4] Effects of hypercapnia

Hypercapnia produced no change in heart rate in the presence of halothane, although there were significant decreases in mean arterial pressure and total peripheral resistance (Table 8.7). There was a significant increase in cardiac output, although less than that seen in the absence of halothane. Colonic blood flow increased by 31%, while colonic vascular resistance decreased by 35% (Table 8.8). The corresponding changes prior to halothane administration were 55% and 39%.

In contrast to the effect of hypocapnia, both colonic and total peripheral resistances behaved in a similar fashion in response to hypercapnia, irrespective of the presence of halothane. There was no significant change in colonic oxygen consumption in response to hypercapnia. Unlike the response to hypocapnia, the effect of hypercapnia on colonic blood flow was proportionately less in the presence of halothane (Figure 8.3).

Lactate concentrations in arterial, mixed venous and colonic venous blood decreased significantly in response to hypercapnia in

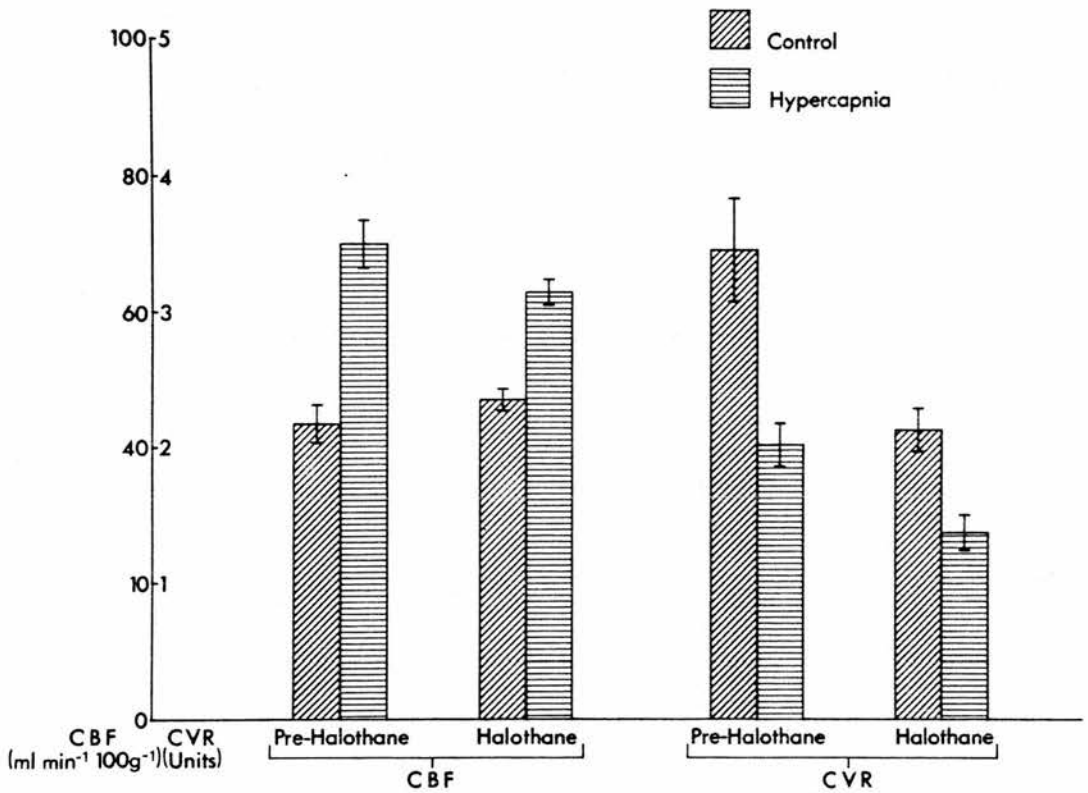
TABLE 8.7 Effects of hypercapnia on systemic haemodynamics and oxygen consumption before and during halothane administration. Values from 11 dogs expressed as mean (sem).

	Before halothane			Halothane		
	Control	p	Hypercapnia	Control	p	Hypercapnia
Heart rate (beat min^{-1})	140.9 (5.3)	n.s.	140.0 (6.2)	113.2 (5.5)	n.s.	112.3 (7.0)
Mean arterial pressure (mm Hg)	140.9 (5.3)	n.s.	140.0 (6.2)	99.1 (5.3)	< 0.005	85.6 (7.2)
Cardiac output (litre min^{-1})	4.46(0.31)	< 0.0001	5.66(0.38)	3.89(0.19)	< 0.05	4.54(0.31)
Total peripheral resistance (unit)	30.2 (3.6)	n.s.	26.1 (2.8)	26.3 (2.2)	< 0.001	19.4 (1.7)
Total oxygen consumption (ml min^{-1})	173.3 (13.4)	n.s.	243.4 (40.2)	175.2 (14.0)	n.s.	225.5 (23.8)

TABLE 8.8 Effects of hypercapnia on colonic haemodynamics and oxygen consumption before and during halothane administration. Values from 11 dogs expressed as mean (sem).

	Before halothane			Halothane		
	Control	p	Hypercapnia	Control	p	Hypercapnia
Colon blood flow ($ml\ min^{-1}\ 100\ g^{-1}$)	43.7 (2.9)	< 0.0001	67.8 (3.9)	47.2 (1.9)	< 0.0001	61.8 (2.1)
Colon vascular resistance (unit)	3.49(0.35)	< 0.001	2.14(0.19)	2.15(0.15)	< 0.0001	1.40(0.12)
Colon oxygen consumption ($ml\ min^{-1}\ 100\ g^{-1}$)	1.04(0.15)	n.s.	1.01(0.21)	0.81(0.25)	n.s.	1.12(0.22)

TABLE 8.8



Changes in colonic blood flow (CBF) and colonic vascular resistance (CVR) resulting from hypercapnia before and during administration of halothane. Values are from 11 dogs. Blocks represent mean values at normal P_aCO_2 (diagonal hatch) and during hypercapnia (horizontal hatch). Bars represent sem. Significance values shown in Table 8.8.

TABLE 8.9 Effects of hypercapnia on blood lactate and pyruvate concentrations during halothane administration. Values from 11 dogs expressed as mean (sem).

	Normocapnia	p	Hypercapnia
Arterial lactate concentration (μmol litre^{-1})	808.8 (117.1)	< 0.005	520.0 (65.6)
Arterial pyruvate concentration (μmol litre^{-1})	65.5 (6.7)	n.s.	68.6 (7.4)
Arterial lactate/pyruvate ratio	12.57 (1.99)	< 0.01	7.96 (1.18)
Mixed venous lactate concentration (μmol litre^{-1})	827.1 (156.1)	< 0.05	474.3 (83.5)
Mixed venous pyruvate concentration (μmol litre^{-1})	69.9 (7.1)	< 0.05	56.7 (5.0)
Mixed venous lactate/pyruvate ratio	11.88 (2.34)	n.s.	8.43 (1.78)
Colon lactate concentration (μmol litre^{-1})	788.8 (102.5)	< 0.05	557.5 (62.3)
Colon pyruvate concentration (μmol litre^{-1})	69.8 (12.6)	n.s.	60.3 (7.4)
Colon lactate/pyruvate ratio	12.57 (2.03)	n.s.	9.51 (0.75)

the presence of halothane (Table 8.9). There was a significant decrease in pyruvate concentration in mixed venous blood. There appeared to be decreases in lactate/pyruvate ratios in blood from all sampling sites, but only the decreased ratio in arterial blood was statistically significant. There were no significant differences in lactate or pyruvate concentrations, or the lactate/pyruvate ratios, between arterial, mixed venous and colonic venous blood irrespective of the arterial P_{CO_2}. The lactate and pyruvate values before and during hypercapnia in the same animals prior to the administration of halothane have been presented in Chapter Five (Table 5.7). There were no significant differences between corresponding values before and during halothane administration.

[8.4] DISCUSSION

[8.4.1] The effects on systemic circulation

Halothane depresses cardiac output and arterial pressure in a dose-dependent manner (Deutsch et al., 1962; Prys-Roberts et al., 1974). Prys-Roberts and his colleagues found that cardiac output decreased from 3.61 litre min^{-1} in humans during IPPV with oxygen alone to 2.31 and 1.47 litre min^{-1} during IPPV with an inspired halothane concentration of 1% and 2% respectively. Mean arterial pressure decreased by 26% and 49% compared with control measurements during administration of 1% and 2% halothane respectively. Heart rate did not change significantly, and total peripheral resistance was also unaffected, although other investigators (Deutsch et al., 1962; Eger et al., 1970) have found a small (less than 10%) decrease to occur in total peripheral resistance when halothane is administered at between 1 and 2 MAC during normocapnia, and depression of heart rate has also

been reported (Hickey and Eger, 1981). Vatner and Smith (1974) found that administration of halothane 1% in dogs resulted in average decreases in heart rate of 24%, in mean arterial pressure of 30% and in left ventricular peak dP/dt of 40%.

In the present study, in which an initial inspired concentration of 2% halothane was subsequently reduced to approximately 1%, the dogs were receiving halothane at a concentration of just over 1 MAC. Heart rate decreased by 14%, mean arterial pressure by 32%, and cardiac output by 20%. There was a reduction of 14% in total peripheral resistance. The changes were therefore in keeping with the previously reported effects of halothane during IPPV at normocapnia. The major differences between the hypotension produced by halothane and that resulting from spinal nerve block were in respect of cardiac output and total peripheral resistance. During spinal nerve block, the reduction of arterial pressure was achieved almost entirely by vasodilatation. In contrast, halothane produced hypotension predominantly by a reduction of cardiac output.

The effects of carbon dioxide changes on the circulation have been discussed in Chapter Five. Hypercapnia during spontaneous ventilation with halothane in man results in increases in cardiac output, arterial pressure and heart rate, and a decrease in total peripheral vascular resistance (Bahlman et al., 1972). In the present study, hypercapnia during IPPV with halothane produced different effects. Cardiac output did increase and total peripheral resistance decreased, but heart rate was unchanged, and mean arterial pressure decreased. These changes were not dissimilar to those which occurred in response to hypercapnia during spinal nerve block (Chapter Seven).

[**8.4.2**] The effects on colonic circulation

Halothane at an inspired concentration of 1.2 to 1.6% has been reported to produce a 29% decrease in hepatic blood flow, with no change in splanchnic vascular resistance (Epstein et al., 1966). The reduction in flow was therefore attributed to decreased perfusion pressure and a reduction in cardiac output. An increase in P_aCO_2 from 5.5 to 7.6 kPa resulted in a decrease in splanchnic vascular resistance and an increase in hepatic blood flow.

Vatner and Smith (1974) reported that mesenteric blood flow decreased by 56% in dogs and by 65% in primates in response to the administration of halothane 1%, while mesenteric vascular resistance increased by 41% in dogs and by 49% in primates. The changes were much more marked in the mesenteric circulation than in the coronary, renal or iliac vascular beds. These authors injected halothane (0.1 ml in 10 ml blood) directly into the mesenteric artery, and observed an increase of 156% in mesenteric blood flow. This increase was not affected by adrenergic blockade with propranolol or phentolamine, by cholinergic blockade with atropine, or by histaminergic blockade with tripelennamine. They concluded that halothane acted directly to produce vasodilatation of peripheral blood vessels, although the concentration administered was very much greater than that achieved in arterial blood during inhalation anaesthesia. The finding of vasoconstriction of the mesenteric vascular bed during halothane anaesthesia was explained on the basis of baroreceptor stimulation from the hypotension resulting from halothane administration, with a possible contribution from vasopressin release induced by halothane (Akester and Brody, 1969).

The findings of the present study do not support those of

Vatner and Smith. During inhalation of 1% halothane, colonic vascular resistance decreased by 40%, and colonic blood flow increased significantly despite the reductions in mean arterial pressure and cardiac output. Baroreceptor activity is inhibited by halothane (Whayne et al., 1971), and the fact that heart rate decreased does not lend credence to Vatner and Smith's hypothesis.

The changes in colonic haemodynamics in response to alterations in P_aCO_2 during halothane anaesthesia were qualitatively the same as those reported in the splanchnic circulation as a whole (Epstein et al., 1966), and those found during spinal nerve block (Chapter Seven). However, there were quantitative differences between halothane and spinal nerve block. During spinal nerve block, both hypocapnia and hypercapnia resulted in larger alterations in colonic vascular resistance than had occurred before the block was performed. When halothane was administered, the increase in colonic vascular resistance in response to hypocapnia was of greater magnitude than that found in the absence of halothane, while the decrease associated with hypercapnia was less during halothane administration. These differences were reflected in changes in colonic blood flow, and may be the result of depression by halothane of the response of the sympathetic nervous system to an elevated P_{CO_2}. A direct depression by halothane of reactivity of vascular smooth muscle in the colon would have tended to reduce the degree of vasoconstriction associated with hypocapnia.

[**8.4.3**] <u>The effects on colonic oxygenation</u>

Andreen, Irestedt and Thulin (1975) found a reduction in oxygen uptake in the splanchnic circulation together with a reduction in

blood flow during halothane anaesthesia. In the present study, colonic blood flows tended to be higher at a given P_aCO_2 after halothane than before. Although colonic venous lactate concentration increased significantly when halothane was first administered, it decreased subsequently to values lower than at the corresponding point in the experiment before halothane administration. At no time did lactate concentrations exceed the upper limit of the normal range. Colonic oxygen consumption tended to be lower during halothane administration, although the differences were not statistically significant. Colonic venous P_{O_2} and oxygen content were statistically significantly decreased during halothane administration, but these differences were very small, and are unlikely to have been of physiological importance. There therefore seemed to be no evidence of a significant degree of anaerobic metabolism associated with halothane administration, irrespective of the arterial P_{CO_2}.

[**8.4.4**] Clinical significance

During spontaneous ventilation with halothane, arterial P_{CO_2} tends to increase as a result of hypoventilation. An anaesthetic technique of this type is rarely used for major abdominal surgery because of the lack of adequate muscle relaxation, although it is employed by some anaesthetists for procedures such as closure of colostomy. In this situation, the combination of halothane and a degree of hypercapnia may have theoretical advantages, although the effects are presumably confined to the intra-operative period. Most abdominal surgery is undertaken during anaesthesia in which muscle relaxants are employed, and the lungs ventilated artificially. Many anaesthetists choose to hyperventilate the lungs in order to inhibit

respiratory drive and diaphragmatic movement. The results of this study suggest that any increase in blood flow to the colon resulting from the administration of halothane may be negated by the use of a technique resulting in hypocapnia.

The combination of spinal nerve block and light general anaesthesia with spontaneous ventilation of halothane has been described in Chapter Three. If all the relevant factors have additive effects, then the combination of spinal nerve block, halothane and modest hypercapnia may be presumed to result in large increases in colonic blood flow.

CHAPTER NINE

CLINICAL SIGNIFICANCE

[9.1] INTRODUCTION

The purpose of the studies presented in this thesis was to investigate the effects which anaesthetic techniques, and other peri-operative factors which may be influenced by the anaesthetist, might have on patients undergoing surgery of the colon. In Chapter One, two main areas which warranted investigation were outlined; factors which affect contractility and may increase tension within the wall or within the lumen of the colon, and factors which affect blood supply. The present studies have concentrated on blood flow, although the results of the clinical study presented in Chapter Three suggested that the choice of opioid may influence the outcome of patients undergoing a colonic anastomosis, possibly as a result of effects on intraluminal pressures, and is worthy of further investigation.

[9.2] COLONIC BLOOD FLOW

The method described in Chapter Four for the measurement of colonic blood flow, and used for the investigations presented in subsequent chapters, was new but was compared carefully with a recognised technique in order to validate the results obtained. A decision was made to use the 90 sec washout curves rather than the 18 min curves because of the complex mathematical analysis required for the latter, and because of the possibility of flow changing during the course of the measurement period. However, the use of the shorter

washout curve provided values for total colonic blood flow only. As a result, the influence on the distribution of blood within the colon of factors which altered total colonic blood flow was not assessed. It is not known whether alterations in blood flow to the mucosa or the muscularis of the colon are of more importance in influencing healing after an anastomosis. However, the few studies which have investigated distribution of blood flow within the colon suggest that changes in the mucosa/submucosa and in the muscularis tend to increase and decrease in parallel with alterations in total flow (Kvietys and Granger, 1982).

The studies of blood flow were undertaken on normal colon. However, an anastomosis may have a reduced blood flow, either because of impairment of the arterial blood supply as a result of resection (Everett, 1974), or because of local oedema caused by surgical manipulation and insertion of sutures. Thus, it remains uncertain whether the alterations in colonic blood flow which were found in the experiments described in this thesis would occur to the same degree at an anastomotic site. It was intended that, after the normal colon had been investigated, a subsequent series of experiments would be performed in which the colon would be transected and anastomosed, and the blood flow at the anastomosis itself measured by positioning the anastomotic site under the scintillation counter. However, when this was attempted, it was found that the venous drainage of the greyhound colon occurs in a cephalad direction only. Thus, the inferior segment of the anastomosed colon was deprived of its venous drainage, and became grossly congested.

The interpretation of the results of the blood flow experiments in terms of the possible influence on anastomotic blood flow and

healing which might be produced by the factors studied is therefore difficult. However, the likelihood exists that although blood flow to an anastomosis may differ in absolute terms from that to normal colon, factors which alter colonic blood flow will produce changes in flow to an anastomotic suture line. Measurement of blood flow to an anastomosis appears worthy of further study, and such investigations may be aided by the use of the non-invasive laser-Doppler velocimetric method of measurement of intestinal blood flow described by Shepherd and Riedel (1982).

[9.3] THE EFFECTS OF ANAESTHETIC AND OTHER PERI-OPERATIVE FACTORS

The results of the clinical study presented in Chapter Three were inconclusive, but suggest that both spinal nerve block and opioid administration warrant further investigation in respect of their influence on the outcome of colonic anastomoses. Because spinal nerve block or opioids may be used to provide analgesia for 48 - 72 hr in the post-operative period, any beneficial or adverse effects might be of greater importance than those of factors applicable only during surgery or in the immediate post-operative period.

The studies described in the second half of the thesis have demonstrated that colonic blood flow is influenced significantly by alterations in carbon dioxide tension, by moderate hypovolaemia, by spinal nerve block and by halothane. In addition, the relationships between some combinations of these factors have been demonstrated. Although the effects of hypovolaemia had been studied previously, the methods used had been more invasive. None of the other factors had been investigated before, and the findings of the present studies are, at the very least, of scientific interest.

If alterations in blood flow associated with these factors do affect anastomotic healing, is their influence significant in comparison with the many other variables (e.g. age, disease, anaemia, site of anastomosis) discussed in Chapter One? Andreen (1982) has drawn attention to the fact that while anaesthesia has some effect on splanchnic and hepatic blood flow, many other risk factors exist in patients undergoing surgery. Kaufman (1984) concluded that the hazards of anaesthetic agents and techniques on the integrity of a colonic anastomosis are more theoretical than practical. This may be true. However, a large part of medical practice is rightly based on theory. While other factors may be outwith the control of medical staff, the anaesthetist is in a position to influence blood flow to an anastomosis. It appears reasonable to conclude that the avoidance of factors which reduce the oxygen supply to an anastomosis is desirable, while the provision of an enhanced blood flow could be advantageous to patients in whom oxygenation of an anastomosis is compromised.

REFERENCES

Akester, J. M., and Brody, M. J. (1969). Mechanism of vascular resistance changes produced in skin and muscle by halothane.
Journal of Pharmacology and Experimental Therapeutics, **170**, 287 - 293.

Andreen, M. (1982). Inhalation versus intravenous anaesthesia. Effects on the hepatic and splanchnic circulation.
Acta Anaesthesiologica Scandinavica, **Suppl. 75**, 25 - 31.

Andreen, M., Irestedt, L., and Thulin, L. (1975). The effect of controlled halothane anaesthesia on splanchnic oxygen consumption in the dog.
Acta Anaesthesiologica Scandinavica, **19**, 238 - 244.

Bacaner, B. M. (1966). Quantitative measurement of regional colon blood flow in the normal and pathological human bowel.
Gastroenterology, **51**, 764 - 777.

Bahlman, S. H., Eger, E. I., Halsey, M. J., Stevens, W. C., Shakespeare, T. F., Smith, N. T., Cromwell, T. H., and Fourcade, H. (1972). Cardiovascular effects of halothane in man during spontaneous ventilation.
Anesthesiology, **36**, 494 - 502.

Bailey, M. J., Johnston, C. L. W., Yates, C. P. J., Somerville, P. G., and Dormandy, J. A. (1979). Preoperative haemoglobin as predictor of outcome of diabetic amputations.
Lancet, **2**, 168 - 170.

Bárány, F., and Jacobson, B. (1964). Endoradiosonde study of propulsion and pressure activity induced by test meals, Prostigmine, and diphenoxylate in the small intestine.
Gut, **5**, 90 - 95.

Bassingthwaighte, J. B., Strandell, T., and Donald, D. E. (1968). Estimation of coronary blood flow by washout of diffusible indicators.
Circulation Research, **23**, 259 - 278.

Bavister, P. H., and Longnecker, D. E. (1979). Influence of anaesthetic agents on the survival of rats following acute ischaemia of the bowel.
British Journal of Anaesthesia, **51**, 921 - 925.

Bell, C. M. A., and Lewis, C. B. (1968). Effect of neostigmine on integrity of ileorectal anastomoses.
British Medical Journal, **3**, 587-588.

Bigler, D., Hjortsø, N-C., and Kehlet, H. (1985). Disruption of colonic anastomosis during continuous epidural analgesia.
Anaesthesia, **40**, 278 - 280.

Birnbaum, D., Ben-Menachem, J., and Schwartz, A. (1970). The influence of oral diazepam on gastrointestinal motility.
American Journal of Proctology, **21**, 263 - 267.

Bond, J. H., and Levitt, M. D. (1979). Use of microspheres to measure small intestinal villus blood flow in the dog.
American Journal of Physiology, **236**, E577.

Bond, J. H., and Levitt, M. D. (1980). Effect of glucagon on gastrointestinal blood flow of dogs in hypovolemic shock.
American Journal of Physiology, **238**, G434 - G439.

Bond, J. H., Prentiss, R. A., and Levitt, M. D. (1980). The effect of anesthesia and laparotomy on blood flow to the stomach, small bowel and colon of the dog.
Surgery, **87**, 313 - 318.

Bunch, G. A. (1971). The intestinal response to surgery.
British Journal of Surgery, **58**, 755 - 759.

Burnstock, G. (1972). Purinergic nerves.
Pharmacological Reviews, **24**, 509 - 581.

Burnum, J. F., Hickam, J. B., and McIntosh, H. D. (1954). The effect of hypocapnia on arterial blood pressure.
Circulation, **9**, 89 - 95.

Burstein, C. L. (1939). Effect of spinal anesthesia on intestinal activity.
Proceedings of the Society for Experimental Biology and Medicine, **42**, 291 - 293.

Carmichael, M. J., Weisbrodt, N. W., and Copeland, E. M. (1977). Effect of abdominal surgery on intestinal myoelectric activity in the dog.
American Journal of Surgery, **133**, 34 - 38.

Casale, F. F. (1970). Convulsions following surgery.
British Journal of Anaesthesia, **42**, 1024.

Chambers, W. A., Edstrom, H. H., and Scott, D. B. (1981). Effect of baricity on spinal anaesthesia with bupivacaine.
British Journal of Anaesthesia, **53**, 279 - 282.

Chassin, J. L. (1978). Stapling technique for esophagogastrectomy after esophagogastric resection.
American Journal of Surgery, **136**, 399 - 404.

Chidsey, C. A., Fritts, H. W., Hardewig, A., Richards, D. W., and Cournand, A. (1959). Fate of radioactive krypton (Kr^{85}) introduced intravenously in man.
Journal of Applied Physiology, **14**, 63 - 66.

Chien, S., Dellenback, R. J., Usami, S., Burton, D. A., Gustavson, P. F., and Magazinovic, V. (1973). Blood volume, hemodynamic, and metabolic changes in hemorrhagic shock in normal and splenectomised dogs.
American Journal of Physiology, **225**, 866 - 879.

Child, C. S. (1984). Prevention of neostigmine-induced colonic activity.
Anaesthesia, **39**, 1083 - 1085.

Chiu, C. J., McArdle, A. H., Brown, R., Scott, H. J., and Gurd, F. N. (1970). Intestinal mucosal lesions in low flow states.
Archives of Surgery, **101**, 478-483.

Chou, C. C., and Dabney, J. M. (1967). Interrelation of ileal wall compliance and vascular resistance.
American Journal of Digestive Diseases, **12**, 1198 - 1208.

Chou, C. C., and Gallavan, R. H. (1982). Blood flow and intestinal motility.
Federation Proceedings, **41**, 2090 - 2095.

Chou, C. C., and Grassmick, B. (1978). Motility and blood flow distribution within the walls of the gastrointestinal tract.
American Journal of Physiology, **235**, H34 - H39.

Cohen, P. J. (1972). The metabolic function of oxygen and biochemical lesions of hypoxia.
Anesthesiology, **37**, 148 - 177.

Cohen, R. A., and Coffman, J. D. (1980). Naloxone reversal of morphine-induced peripheral vasodilatation.
Clinical Pharmacology and Therapeutics, **28**, 541 - 544.

Cullen, D. J., Eger, E. I., and Gregory, G. A. (1969). The cardiovascular effects of carbon dioxide in man, conscious and during cyclopropane anesthesia.
Anesthesiology, **31**, 407 - 413.

Davidson, D. F. (1978). Analysis for lactate and pyruvate with the LKB 8600 reaction rate analyser.
Clinical Chemistry, **24**, 512 - 513.

Defalque, R. J. (1962). Compared effects of spinal and extradural anesthesia upon blood pressure.
Anesthesiology, **23**, 627 - 630.

Deutsch, S., Linde, H. W., Dripps, R. D., and Price, H. L. (1962). Circulatory and respiratory actions of halothane in normal man.
Anesthesiology, **23**, 631 - 638.

Douglas, I. H. S., Macdonald, J. A. E., Milligan, G. F., Mellon, A., and Ledingham, I. McA. (1975). A comparison of methods for the measurement of cardiac output and blood oxygen content.
British Journal of Anaesthesia, **47**, 443 - 450.

Duffy, T. E., Nelson, S. R., and Lowry, O. H. (1972). Cerebral carbohydrate metabolism during acute hypoxia and recovery.
Journal of Neurochemistry, **19**, 959 - 977.

Dunphy, J. E. (1970). The cut gut.
American Journal of Surgery, **119**, 1 - 8.

Eade, M. N., and Ginn, R. W. (1978). The distribution of blood flow along the small intestine of the dog.
Proceedings of the Society for Experimental Biology and Medicine, **157**, 390 - 392.

Eger, E. I., Brandstater, B., Saidman, L. J., Regan, M. J., Severinghaus, J. W., and Munson, E. S. (1965). Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog.
Anesthesiology, **26**, 771 - 777.

Eger, E. I., and Saidman, L. J. (1965). Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax.
Anesthesiology, **26**, 61 - 66.

Eger, E. I., Smith, N. T., Stoelting, R. K., Cullen, D. J., Kadis, L. B., and Whitcher, C. E. (1970). Cardiovascular effects of halothane in man.
Anesthesiology, **32**, 396 - 409.

Ekbom, G., Schulte, W. J., Condon, R. E., Woods, J. H., and Cowles, V. (1980). Effects of narcotic analgesics on bowel motility in subhuman primates.
Journal of Surgical Research, **28**, 293 - 296.

Epstein, R. M., Deutsch, S., Cooperman, L. H., Clement, A. H., and Price, H. L. (1966). Splanchnic circulation during halothane anesthesia and hypercapnia in normal man.
Anesthesiology, **27**, 654 - 661.

Epstein, R. M., Wheeler, H. O., Frumin, M. J., Halif, D. V., Papper, E. M., and Bradley, S. E. (1961). The effect of hypercapnia on estimated hepatic blood flow, circulating splanchnic volume and hepatic sulfobromophthalein clearance during general anesthesia in man.
Journal of Clinical Investigation, **40**, 592 - 598.

Everett, W. G. (1974). Sutures, incisions and anastomoses.
Annals of the Royal College of Surgeons of England, **55**, 31 - 38.

Fell, D., Chmielewski, A., and Smith, G. (1982). Postoperative analgesia with controlled-release morphine sulphate: comparison with intramuscular morphine.
British Medical Journal, **285**, 92 - 94.

Fisher, W. D., Heimbach, D. W., McArdle, C. S., Maddern, M., Hutcheson, M. M., and Ledingham, I. McA. (1973). A circulating depressant effect following canine haemorrhagic shock.
British Journal of Surgery, **60**, 392 - 394.

Foëx, P. (1980). Effects of carbon dioxide on the systemic circulation. In:
The Circulation in Anaesthesia, ed. Prys-Roberts, C., pp. 295 - 309. Oxford: Blackwell.

Foëx, P., and Fordham, R. M. M. (1972). Intrinsic myocardial recovery from the negative inotropic effects of acute hypercapnia.
Cardiovascular Research, **6**, 257 - 262.

Folkow, B. (1949). Intravascular pressure as factor regulating tone of the small vessels.
Acta Physiologica Scandinavica, **17**, 289 - 310.

Ganong, W. F. (1979).
Review of Medical Physiology, 9th ed., p. 479. Los Altos: Lange.

Garry, R. C. (1933). Nervous control of caudal region of large bowel in cat.
Journal of Physiology (London), **77**, 422 - 431.

Gilmour, D. G., Aitkenhead, A. R., and Ledingham, I. McA. (1980). Results of ^{133}Xenon clearance studies in the greyhound colon. In: Gastrointestinal Mucosal Blood Flow, ed. Fielding, L. P., pp. 219 - 229. Edinburgh: Churchill Livingstone.

Goligher, J. C., Graham, N. G., and DeDombal, F. T. (1970). Anastomotic dehiscence after anterior resection of rectum and sigmoid.
British Journal of Surgery, **57**, 109-118.

Goligher, J. C., Morris, C., McAdam, W. A. F., DeDombal, F. T., and Johnston, D. (1970). A controlled trial of inverting versus everting intestinal suture in clinical large bowel surgery.
British Journal of Surgery, **57**, 817 - 822.

Grace, R. H., (1971). The handling of water and electrolytes by the small bowel following the relief of intestinal obstruction.
British Journal of Surgery, **58**, 760 - 764.

Grayson, J. (1951). The measurement of intestinal blood flow in man.
Journal of Physiology (London), **114**, 419 - 434.

Green, H. D., and Kepchar, J. H. (1959). Control of peripheral resistance in major systemic vascular beds.
Physiological Reviews, **39**, 617 - 686.

Green, H. D., Lewis, R. N., Nickerson, N. D., and Heller, A. L. (1944). Blood flow, peripheral resistance, and vascular tonus with observations on relationship between blood flow and cutaneous temperature.
American Journal of Physiology, **141**, 518 - 536.

Greene, N. M. (1981).
Physiology of Spinal Anaesthesia, 3rd ed., p. 256. Baltimore: Williams and Wilkins.

Grim, E., and Lindseth, E. O. (1958). Distribution of blood flow to the tissues of the small intestine of the dog.
University of Minnesota Medical Bulletin, **30**, 138 - 145.

Gruber, U. F. (1970). Recent developments in the investigation and treatment of hypovolaemic shock.
British Journal of Hospital Medicine, **4**, 631 - 638.

Haglund, U. (1973). The small intestine in hypotension and haemorrhage. An experimental cardiovascular study in the cat.
Acta Physiologica Scandinavica, **Suppl. 387**, 1-37.

Haglund, U., Hultén, L., Åhrén, C., and Lundgren, O. (1975). Mucosal lesions in the human small intestine in shock.
Gut, **16**, 979 - 984.

Hall, L. W. (1971).
Veterinary Anaesthesia and Analgesia, 7th ed., p. 181. London: Baillère, Tindall, and Cassell.

Halter, J. B., Pflug, A. E., and Porter, D. (1977). Mechanism of plasma catecholamine increases during surgical stress in man.
Journal of Clinical Endocrinology and Metabolism, **45**, 936 - 944.

Hanson, K. M. (1973). Hemodynamic effects of distention of the dog small intestine.
American Journal of Physiology, **225**, 456 - 460.

Hanson, K. M., and Johnson, P. C. (1967). Pressure-flow relationships in isolated dog colon.
American Journal of Physiology, **212**, 574 - 578.

Hanson, K. M., and Moore, F. T. (1969a). Pressure-volume relationships and blood flow in the distended colon.
American Journal of Physiology, **217**, 35 - 39.

Hanson, K. M., and Moore, F. T. (1969b). Effects of intraluminal pressure in the colon on its vascular pressure/flow relationships.
Proceedings of the Society for Experimental Biology and Medicine, **131**, 373 - 376.

Harp, J. R., and Wollman, H. (1973). Cerebral metabolic effects of hyperventilation and deliberate hypotension.
British Journal of Anaesthesia, **45**, 256 - 262.

Harper, A. M., and Glass, H. I. (1965). Effect of alterations in the arterial carbon dioxide tension on the blood flow through the cerebral cortex at normal and low arterial blood pressures.
Journal of Neurology, Neurosurgery and Psychiatry, **28**, 449 - 452.

Healy, T. E. J., Foster, G. E., Evans, D. F., and Syed, A. (1981). Effect of some i.v. anaesthetic agents on canine gastrointestinal motility.
British Journal of Anaesthesia, **53**, 229 - 233.

Hickey, R. F., and Eger, E. I. (1981). Circulatory pharmacology of inhaled anesthetics. In:
Anesthesia, ed. Miller, R. D., pp. 331 - 348. New York: Churchill Livingstone.

Huckabee, W. E. (1958). Relationships of pyruvate and lactate during anaerobic metabolism. I: Effects of infusion of pyruvate or glucose and of hyperventilation.
Journal of Clinical Investigation, **37**, 244 - 254.

Hughes, R. L., Mathie, R. T., Campbell, D., and Fitch, W. (1979a). Effect of hypercarbia on hepatic blood flow and oxygen consumption in the greyhound.
British Journal of Anaesthesia, **51**, 289 - 296.

Hughes, R. L., Mathie, R. T., Fitch, W., and Campbell, D. (1979b). Liver blood flow and oxygen consumption during hypocapnia and IPPV in the greyhound.
Journal of Applied Physiology, **47**, 290 - 295.

Hultén, L. (1969). Extrinsic nervous control of colonic motility and blood flow.
Acta Physiologica Scandinavica, **Suppl. 335**, 1 - 116.

Hultén, L., Jodal, M., Lindhagen, J., and Lundgren, O. (1976a). Colonic blood flow in cat and man as analysed by an inert gas washout technique.
Gastroenterology, **70**, 36 - 44.

Hultén, L., Jodal, M., Lindhagen, J., and Lundgren, O. (1976b). Blood flow in the small intestine of cat and man as analysed by an inert gas washout technique.
Gastroenterology, **70**, 45 - 51.

Hultén, L., Lindhagen, J., and Lundgren, O. (1977). Sympathetic nervous control of intramural blood flow in the feline and human intestines.
Gastroenterology, **72**, 41 - 48.

Hultén, L., Lindhagen, J., Lundgren, O., Fasth, S., and Ahrén, C. (1977). Regional intestinal blood flow in ulcerative colitis and Crohn's disease.
Gastroenterology, **72**, 388 - 396.

Hunt, T. K., and Pai, M. P. (1972). The effect of varying ambient oxygen tensions on wound metabolism and collagen synthesis.
Surgery, Gynecology and Obstetrics, **135**, 561 - 567.

Immink, W. F. G. A., Beijer, H. J. M., and Charbon, G. A. (1976). Hemodynamic effects of norepinephrine and isoprenaline in various regions of the canine splanchnic area.
Pflugers Archiv. European Journal of Physiology, **365**, 107 - 118.

Irvin, T. T., and Goligher, J. C. (1973). Aetiology of disruption of intestinal anastomoses.
British Journal of Surgery, **60**, 461 - 464.

Johansson, B., Linder, E., and Seeman, T. (1964). Collateral blood flow in the myocardium of dogs measured with krypton^{85}.
Acta Physiologica Scandinavica, **62**, 263 - 270.

Johnson, E. E. (1975). Splanchnic hemodynamic response to passive hyperventilation.
Journal of Applied Physiology, **38**, 156 - 162.

Kampp, M., and Lundgren, O. (1968). Blood flow and flow distribution in the small intestine of the cat as analysed by the Kr^{85} washout technique.
Acta Physiologica Scandinavica, **72**, 282 - 297.

Kampp, M., Lundgren, O., and Sjösstrand, J. (1968). On the components of the Kr^{85} washout curves from the small intestine of the cat.
Acta Physiologica Scandinavica, **72**, 257 - 281.

Karim, S. M. (1965). Sympathetic ß-receptor blocking action of methoxamine.
British Journal of Pharmacology, **24**, 365 - 374.

Kaufman, L. (1982). Anastomosis and the anaesthetist. In:
Anaesthesia: Review 1., ed. Kaufman, L., p. 77. Edinburgh: Churchill Livingstone.

Kaufman, L. (1984). Abdominal anaesthesia, In:
Anaesthesia: Review 2., ed. Kaufman, L., p. 217. Edinburgh: Churchill Livingstone.

Kelman, G. R. (1966). Digital computer subroutine for the conversion of oxygen tension into saturation.
Journal of Applied Physiology, **21**, 1375 - 1376.

Kelman, G. R. (1977).
Applied Cardiovascular Physiology, 2nd ed., p.216. London: Butterworth.

Kelman, G. R., and Kennedy, B. R. (1971). Cardiovascular effects of pancuronium in man.
British Journal of Anaesthesia, **43**, 335 - 338.

Kelman, G. R., and Nunn, J. F. (1966). Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH and base excess for time and temperature.
Journal of Applied Physiology, **21**, 1484 - 1490.

Kennedy, W. F., Bonica, J. J., Akamatsu, T. J., Ward, R. J., Martin, W. E., and Grinstein, A. (1968). Cardiovascular and respiratory effects of subarachnoid block in the presence of acute blood loss.
Anesthesiology, **29**, 29 - 35.

Kerr, J. C., and Swan, K. G. (1981). Adrenergic stimulation and blockade in colonic circulation of the rhesus monkey.
American Journal of Physiology, **240**, G25 - G31.

Kety, S. S. (1951). The theory and applications of the exchange of inert gas at the lungs and tissues.
Pharmacological Reviews, **3**, 1 - 41.

Kety, S. S. (1960). Theory of blood-tissue exchange and its application to measurement of blood flow.
Methods in Medical Research, **8**, 223 - 227.

Kleinerman, J., Sancetta, S. M., and Hackel, D. B. (1958). Effects of high spinal anesthesia on cerebral circulation and metabolism in man. Journal of Clinical Investigation, **37**, 285 - 293.

Kvietys, P. R., and Granger, D. N. (1981). Effects of solute-coupled fluid absorption on blood flow and oxygen uptake in the dog colon. Gastroenterology, **81**, 450 - 457.

Kvietys, P. R., and Granger, D. N. (1982). Regulation of colonic blood flow.
Federation Proceedings, **41**, 2106 - 2110.

Kvietys, P. R., Miller, T., and Granger, D. N. (1980). Intrinsic control of colonic blood flow and oxygenation.
American Journal of Physiology, **238**, G478 - G484.

Lanciault, G., and Jacobson, E. D. (1976). The gastrointestinal circulation.
Gastroenterology, **71**, 851 - 873.

Leaman, D. M., Levenson, L., Zelis, R., and Shiroff, R. (1978). Effect of morphine on splanchnic blood flow.
British Heart Journal, **40**, 569 - 571.

Ledingham, I. McA., McBride, T. I., Parratt, J. R., and Vance, J. P. (1970). The effect of hypercapnia on myocardial blood flow and metabolism.
Journal of Physiology (London), **210**, 87 - 105.

Lefer, A. M., Glenn, T. M., Lopez-Rasi, A. M., Kiechel, S. F., Ferguson, W. W., and Wangensteen, S. L. (1971). Mechanism of the lack of effect of a beneficial response to inotropic drugs in hemorrhagic shock.
Clinical Pharmacology and Therapeutics, **12**, 506 - 516.

Lewis, G. B. H. (1975) Intestinal distension during nitrous oxide anaesthesia.
Canadian Anaesthetists Society Journal, **22**, 200 - 201.

Libonati, M., Malsch, E., Price, H. L., Cooperman, L. H., Baum, S., and Harp, J. R. (1973). Splanchnic circulation in man during methoxyflurane anesthesia.
Anesthesiology, **38**, 466 - 472.

Lillihei, R. C. (1957). The intestinal factor in irreversible shock.
Surgery, **42**, 1043 - 1054.

Little, R. C., and Smith, C. W. (1964). Cardiovascular response to acute hypocapnia due to overbreathing.
American Journal of Physiology, **206**, 1025 - 1030.

Lundgren, O. (1967). Studies on blood flow distribution and countercurrent exchange in the small intestine.
Acta Physiologica Scandinavica, **Suppl. 303**, 1 - 42.

Lundgren, O., and Haglund, U. (1978). On the chemical nature of the blood borne cardiotoxic material released from the feline small bowel in regional shock.
Acta Physiologica Scandinavica, **103**, 59 - 70.

McLean, A. P. H., Mulligan, G. W., Otton, P., and MacLean, L. D. (1967). Hemodynamic alterations associated with epidural anesthesia.
Surgery, **62**, 79 - 87.

Marshall, B. E., Cohen, P. J., Klingenmaier, C. H., Neigh, J. L., and Pender, J. W. (1971). Some pulmonary and cardiovascular effects of enflurane (Ethrane) anaesthesia with varying P_aCO_2 in man.
British Journal of Anaesthesia, **43**, 996 - 1002.

Marshall, F. N., Pittinger, C. B., and Long, J. P. (1961). Effects of halothane on gastrointestinal motility.
Anesthesiology, **22**, 363 - 366.

Matthews, J. G. W., and Parks, T. G. (1976). Ischaemic colitis in the experimental animal. Role of hypovolaemia in the production of the disease.
Gut, **17**, 677 - 684.

Micflikier, A. B., Bond, J. H., Sircar, B., and Levitt, M. D. (1976). Intestinal villus blood flow measured with carbon monoxide and microspheres.
American Journal of Physiology, **230**, 916 - 919.

Miller, G. H. (1926). Effects of general anesthesia on muscular activity of gastrointestinal tract.
Journal of Pharmacology and Experimental Therapeutics, **27**, 41 - 46.

Moir, D. D. (1968). Blood loss during major vaginal surgery.
British Journal of Anaesthesia, **40**, 233 - 240.

Morgan, M., and Norman, J. (1975). The effect of extradural analgesia combined with light general anaesthesia and spontaneous ventilation on arterial blood gases and physiological dead space.
British Journal of Anaesthesia, **47**, 955 - 961.

Morgenstern, L., Yamakawa, T., Ben-Shoshan, M., and Lippman, H. (1972). Anastomotic leakage after low colonic anastomosis: clinical and experimental aspects.
American Journal of Surgery, **123**, 104 - 109.

Morris, M. E., and Millar, R. A. (1962a). Blood pH/catecholamine relationships: respiratory acidosis.
British Journal of Anaesthesia, **34**, 672 - 681.

Morris, M. E., and Millar, R. A. (1962b). Blood pH/catecholamine relationships: non-respiratory acidosis.
British Journal of Anaesthesia, **34**, 682 - 689.

Moster, W. G., Reier, C. E., Gardier, R. W., and Hamelberg, W. (1969). Cardiac output and postganglionic sympathetic activity during acute respiratory alkalosis.
Anesthesiology, **31**, 28 - 34.

Mueller, R. P., Lynn, R. B., and Sancetta, S. M. (1952). Studies of hemodynamic changes in humans following induction of low and high spinal anesthesia. II. The changes in splanchnic blood flow, oxygen extraction and consumption, and splanchnic vascular resistance in humans not undergoing surgery.
Circulation, **6**, 894 - 901.

Neely, J., and Catchpole, B. (1971). Ileus: the restoration of alimentary-tract motility by pharmacological means.
British Journal of Surgery, **58**, 21 - 27.

Neutze, J. M., Wyler, F., and Rudolph, A. M. (1968). Use of radioactive microspheres to assess distribution of cardiac output in rabbits.
American Journal of Physiology, **215**, 486 - 495.

Norris, H. T., and Sumner, D. S. (1974). Distribution of blood flow to the layers of the small bowel in experimental cholera.
Gastroenterology, **66**, 973 - 981.

Painter, N. S. (1963). The effect of morphine in diverticulosis of the colon.
Proceedings of the Royal Society of Medicine, **56**, 800 - 802.

Painter, N. S., and Truelove, S. C. (1964a). The intraluminal pressure patterns in diverticulosis of the colon. Part II: the effect of morphine.
Gut, **5**, 201 - 213.

Painter, N. S., and Truelove, S. C. (1964b). The intraluminal pressure patterns in diverticulosis of the colon. Part III: the effect of prostigmine.
Gut, **5**, 365 - 369.

Painter, N. S., and Truelove, S. C. (1964c). The intraluminal pressure patterns in diverticulosis of the colon. Part IV: the effect of pethidine and probanthine.
Gut, **5**, 369 - 373.

Pannier, J. L., and Brutsaert, D. L. (1968). Contractility of isolated cat papillary muscle and acid-base changes.
Archives Internationales de Pharmacodynamie et de Thérapie, **172**, 244 - 246.

Pannier, J. L., and Leusen, L. (1968). Contraction characteristics of papillary muscle during changes in acid-base composition of the bathing fluid.
Archives Internationales de Physiologie et de Biochimie, **76**, 624 - 634.

Pappenheimer, J. R. (1952). Peripheral circulation.
Annual Review of Physiology, **14**, 259 - 282.

Parks, T. G. (1970). Rectal and colonic studies after resection of the sigmoid for diverticular disease.
Gut, **11**, 121 - 125.

Pawlik, W., Mailman, D., Shanbour, L. L., and Jacobson, E. D. (1976). Dopamine effects on the intestinal circulation.
American Heart Journal, **91**, 325 - 330.

Petrie, A. (1978).
Lecture Notes on Medical Statistics, pp. 108 - 109. Oxford: Blackwell.

Pflug, A. E., and Halter, J. B. (1981). Effect of spinal anesthesia on adrenergic tone and the neuroendocrine responses to surgical stress in humans.
Anesthesiology, **55**, 120 - 126.

Price, H. L., Deutsch, S., Cooperman, L. H., Clement, A. H., and Epstein, R. M. (1965). Splanchnic circulation during cyclopropane anesthesia in normal man.
Anesthesiology, **26**, 312 - 319.

Prys-Roberts, C., Lloyd, J. W., Fisher, A., Kerr, J. H., and Patterson, T. J. S. (1974). Deliberate profound hypotension induced with halothane: studies of haemodynamics and pulmonary gas exchange. British Journal of Anaesthesia, **46**, 105 - 116.

Pugh, L. G. C., and Wyndham, C. L. (1950). The circulatory effects of high spinal anesthesia in hypertensive and control subjects. Clinical Science, **9**, 189 - 203.

Redderson, C. L., Uy, D., and Anton, A. H. (1974). New techniques for spinal anesthesia in the dog. Anesthesiology, **40**, 187 - 188.

Reivich, M. (1964). Arterial P_{CO_2} and cerebral hemodynamics. American Journal of Physiology, **206**, 25 - 35.

Rennie, J. A., Christofides, N. D., Mitchenere, P., Fletcher, D., Stockley-Leathard, H. L., Bloom, S. R., Johnson, A. G., and Harding Rains, A. J. (1980). Neural and humoral factors in postoperative ileus. British Journal of Surgery, **67**, 694 - 698.

Richardson, D. W., Wasserman, A. J., and Patterson, J. L. (1961). General and regional circulatory responses to change in blood pH and carbon dioxide tension. Journal of Clinical Investigation, **40**, 31 - 43.

Roberts, J. G. (1980). The effects of hypoxia and the systemic circulation during anaesthesia. In: The Circulation in Anaesthesia, ed. Prys-Roberts, C., pp. 311 - 325. Oxford: Blackwell.

Roddie, I. C., Shepherd, J. T., and Whelan, R. F. (1957). Humoral vasodilatation in the forearm during voluntary hyperventilation. Journal of Physiology (London), **137**, 80 - 85.

Roughton, F. J. W., and Severinghaus, J. W. (1973). Accurate determination of O_2 dissociation curve of human blood above 98.7 per cent saturation with data on O_2 solubility in unmodified human blood from 0 degrees C to 37 degrees C.
Journal of Applied Physiology, **35**, 861 - 869.

Ruf, W., Suehiro, G. T., Suehiro, A., Pressler, V., and McNamara, J. J. (1980). Intestinal blood flow at various intraluminal pressures in the piglet with closed abdomen.
Annals of Surgery, **191**, 157 - 163.

Rusca, J. A., Bornside, G. H., and Cohn, I. (1969). Everting versus inverting gastrointestinal anastomoses: bacterial leakage and anastomotic disruption.
Annals of Surgery, **169**, 727 - 732.

Saidman, L. J., Eger, E. I., Munson, E. S., Babad, A. A., and Muallem, M. (1967). Minimum alveolar concentration of methoxyflurane, halothane, ether and cyclopropane in man: correlation with theories of anesthesia.
Anesthesiology, **28**, 994 - 1002.

Sancetta, S. M., Lynn, R. B., Simeone, F. A., and Scott, R. W. (1952). Studies of hemodynamic changes in humans following induction of low and high spinal anesthesia I.
Circulation, **6**, 559 - 571.

Scheuer, J. (1968). The effects of respiratory and metabolic alkalosis on coronary flow, hemodynamics and myocardial carbohydrate metabolism.
Cardiologia (Basel), **52**, 275 - 286.

Scheuer, J., and Berry, N. (1967). Effect of alkalosis on glycolysis in the isolated rat heart.
American Journal of Physiology, **213**, 1143 - 1148.

Schrock, T. R., Deveney, C. W., and Dunphy, J. E. (1973). Factors contributing to leakage of colonic anastomoses.
Annals of Surgery, **173**, 513 - 518.

Sejrsen, P. (1971). Measurement of cutaneous blood flow by freely diffusible radioactive isotopes. Methodological studies on the wash-out of krypton-85 and xenon-133 from the cutaneous tissue in man.
Danish Medical Bulletin, **18**, (Suppl. 3), 9 - 38.

Selkurt, E. E., and Wathen, R. L. (1967). Washout of intra-arterially injected $Xenon^{133}$ from the intestine of the dog as a method for estimating blood flow.
Gastroenterology, **52**, 387 - 390.

Setchell, B. P., Waites, G. M. H., and Thorburn, G. D. (1966). Blood flow in the testis of the conscious ram measured with $krypton^{85}$.
Circulation Research, **18**, 755 - 765.

Shanbour, L. L., and Jacobson, E. D. (1971). Autoregulatory escape in the gut.
Gastroenterology, **60**, 145 - 148.

Shaw, W., and Wolcott, M. W. (1963). A triple-blind study for the clinical evaluation of dextropantoethenyl alcohol and dextropantoethenyl alcohol plus choline chloride.
Surgery, Gynecology and Obstetrics, **116**, 489 - 493.

Shepherd, A. P. (1978). Intestinal O_2 consumption and ^{86}Rb extraction during arterial hypoxia.
American Journal of Physiology, **234** E248 - E251.

Shepherd, A. P., and Riedel, G. L. (1982). Continuous measurement of intestinal mucosal blood flow by laser-Doppler velocimetry.
American Journal of Physiology, **242**, G668 - G672.

Skinhøj, E., and Paulson, O. B. (1969). Carbon dioxide and cerebral circulatory control.
Archives of Neurology, **20**, 249 - 252.

Skinner, D. B. (1976). Esophageal malignancies. Experience with 110 cases.
Surgical Clinics of North America, **56**, 137 - 147.

Stanton-Hicks, M. d'A. (1975). Cardiovascular effects of extradural anaesthesia.
British Journal of Anaesthesia, **47**, 253 - 263.

Stephens, F. O., and Hunt, T. K. (1971). Effect of changes in inspired oxygen and carbon dioxide tension on wound tensile strength.
Annals of Surgery, **173**, 515 - 519.

Stewart, W. B., Stewart, J. M., Izzo, M. J., and Young, L. E. (1950). Age as affecting osmotic and mechanical fragility of dog erythrocytes tagged with radioactive iron.
Journal of Experimental Medicine, **91**, 147 - 159.

Svanvik, J., Tyllström, J., and Wallentin, I. (1968). The effects of hypercapnia and hypoxia on the distribution of capillary blood flow in the denervated intestinal vascular bed.
Acta Physiologica Scandinavica, **74**, 543 - 551.

Szurzewski, J., and Steggerda, F. R. (1968). The effect of hypoxia on the mechanical activity of the canine small intestine.
American Journal of Digestive Diseases, **13**, 178 - 185.

Tagart, R. E. B. (1981). Colorectal anastomosis: factors influencing success.
Journal of the Royal Society of Medicine, **74**, 111 - 118.

Telivuo, L., and Katz, R. L. (1970). The effects of modern intravenous local analgesics on respiration during partial neuromuscular block in man.
Anaesthesia, **25**, 30 - 35.

Tenney, S. M. (1956). Sympatho-adrenal stimulation by carbon dioxide inhalation and the inhibitory effect of carbonic acid on epinephrine response.
American Journal of Physiology, **187**, 341 - 346.

Tenney, S. M. (1960). The effect of carbon dioxide on neurohumoral and endocrine mechanisms.
Anesthesiology, **21**, 674 - 685.

Treissman, D. A. (1980). Disruption of colonic anastomosis associated with epidural anesthesia.
Regional Anesthesia, **5**, 22 - 23.

Vance, J. P., Brown, D. M., and Smith, G. (1973). The effects of hypocapnia on myocardial blood flow and metabolism.
British Journal of Anaesthesia, **45**, 455 - 463.

Vatner, S. F. (1974). Effects of hemorrhage on regional blood flow distribution in dogs and primates.
Journal of Clinical Investigation, **54**, 225 - 235.

Vatner, S. F., and Smith, T. N. (1974). Effect of halothane on left ventricular function and distribution of regional blood flow in dogs and primates.
Circulation Research, **34**, 155 - 167.

Veall, N., and Mallett, B. L. (1965). The partition of trace amounts of Xenon between human blood and brain tissues at 37°C.
Physics in Medicine and Biology, **10**, 375 - 380.

Vickers, M. D., Wood-Smith, F. G., and Stewart, H. C. (1978).
Drugs in Anaesthetic Practice, 5th ed., p. 374. London: Butterworth.

Wangensteen, O. H. (1955).
Intestinal Obstruction, 3rd ed., p. 745. Springfield: Thomas.

Ward, R. J., Bonica, J. J., Freund, F. G., Akamatsu, T., Danziger, F., and Englesson, S. (1965). Epidural and subarachnoid anesthesia: cardiovascular and respiratory effects.
Journal of the American Medical Association, **191**, 275 - 278.

Weil, M. H., and Afifi, A. A. (1970). Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock).
Circulation, **41**, 989 - 1001.

Weisel, W., Youmans, W. B., and Cassels, W. M. (1938). Effect on intestinal motility of cyclopropane anesthesia alone and after morphine-scopolamine premedication.
Journal of Pharmacology and Experimental Therapeutics, **63**, 391 - 399.

Welsh, J. T. (1963). Colon blood flow.
American Journal of Digestive Diseases, **8**, 614 - 622.

Whayne, T. F., Smith, N. T., Eger, E. I., Stoelting, R. K., and Whitcher, C. E. (1971). The effects of halothane anesthesia on reflex cardiovascular responses to simulated diving and the valsalva maneuver.
Anesthesiology, **34**, 262 - 270.

Whitaker, B. L. (1968). Observations on the blood flow in the inferior mesenteric arterial system and the healing of colonic anastomoses.
Annals of the Royal College of Surgeons of England, **43**, 89 - 110.

Whitaker, B. L., Dixon, R. A., and Greatorex, G. (1970). Anastomotic failure in relation to blood transfusion and blood loss.
Proceedings of the Royal Society of Medicine, **63**, 751.

Wilkins, J. L., Hardcastle, J. D., Mann, C. V., and Kaufman, L. (1970). Effects of neostigmine and atropine on motor activity of ileum, colon, and rectum of anaesthetised subjects.
British Medical Journal, **1**, 793 - 794.

Wilmore, D. W., Goodwin, C. W., Aulick, L. H., Powanda, M. C., Mason, A. D., and Pruitt, B. A. (1980). Effect of injury and infection on visceral metabolism and circulation.
Annals of Surgery, **192**, 491 - 504.

Wilson, J. P. (1975). Postoperative motility of the large intestine in man.
Gut, **16**, 689 - 692.

Wilson, S. E., Hiatt, J., Winston, M., and Passaro, E. (1975). Intestinal blood flow: an evaluation by clearance of $Xenon^{133}$ from the canine jejunum.
Archives of Surgery, **110**, 797 - 801.

Wilson, T. H. (1962).
Intestinal Absorption. Philadelphia: Saunders.

Youmans, W. B. (1952). Neural regulation of gastric and intestinal motility.
American Journal of Medicine, **13**, 209 - 226.

Zederfeldt, B. (1957). Studies on wound healing and trauma.
Acta Chirurgica Scandinavica, **Suppl. 224**, 1 - 85.

Zierler, K. L. (1965). Equations for measuring blood flow by external monitoring of radioisotopes.
Circulation Research, **16**, 309 - 321.